Investigating uptake in faecal immunochemical test (FIT) based colorectal cancer screening

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List of abbreviations

ABC	Awareness and Beliefs about Cancer
APC	Annual percentage change
ASR	Age standardised rate
CI	Confidence Interval
CSO	Central Statistics Office
CTC	Computed tomography colonography
DCO	Death certificate only
DNA	Deoxyribonucleic acid
ERUS	Endo-rectal ultrasound
ESP	European Standard Population
EU	European Union
FIT	Faecal immunochemical test
gFOBT	Guaiac-based faecal occult blood Test
GP	General Practitioner
HIQA	Health Information and Quality Authority
HP	Haase Pratschke
HSE	Health Service Executive
HTA	Health Technology Assessment
ICD10	International Classification of Diseases 10th revision
ICERs	Incremental cost-effectiveness ratios
IQR	Inter Quartile Range
LYG	Life years gained
MDM	Multi-disciplinary meetings

MRI	Magnetic resonance imaging
NCRI	National Cancer Registry Ireland
NCSS	National Cancer Screening Service
NSS	National Screening Service
QALY	Quality Adjusted Life Years
RCT	Randomised Control trial
RR	Relative Risks
RS	Relative survival
TDF	Theoretical Domains Framework
TTC-CRC-SP	Tallaght Hospital/ Trinity College Colorectal Cancer Screening Programme
WHO	World Health Organisation

Declaration

I declare that this thesis has not been submitted for another degree at this or at any other University. The work, upon which this thesis is based, was carried out in collaboration with a team of researchers and supervisors who are duly acknowledged in the text of this thesis.

Signed: _____ Date: _____

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Thesis Abstract

Colorectal cancer is a major public health issue, being one of the most diagnosed cancers in men and women and one of the leading causes of cancer related mortality. Almost 2500 people are diagnosed with colorectal cancer each year in Ireland and over 1000 die from the disease. Males are at greater risk of developing and dying from colorectal cancer. Colorectal cancer is a highly treatable disease if detected at an early stage; however the disease can often take more than ten years to exhibit symptoms in those who develop it. Colorectal cancer will often be asymptomatic until signs and symptoms begin to express themselves, and often times this is when the disease has progressed to late stage disease, at which point treatment is more onerous and outcomes are not as good. In late 2013 Ireland began to roll out the National Colorectal Cancer Screening Programme (BowelScreen) using the new faecal immunochemical test (FIT) technology, the first time this technology was to be used in a national population based screening programme. This was the first time males had been invited to take part in a nationally organised cancer screening programme. This thesis investigates uptake of population-based FIT-based colorectal cancer screening and explores factors associated with uptake in males and females with the intent of providing evidence to improve uptake in screening programmes, thereby impacting on the detection and reduction of incidence and mortality from colorectal cancer within the population. The thesis presents an epidemiological study of colorectal cancer in Ireland during 1994 to 2010, prior to the establishment of the national colorectal cancer screening programme. A systematic review provides evidence that FIT uptake is low internationally, and furthermore that uptake using FIT screening is significantly lower in males, but importantly that it is not the screening programme design or organisation that influences uptake differences in

males and females. In attempting to understand drivers of non-use a qualitative study of users and non-users of a population based FIT-based screening programme was also carried out. Results indicated a number of factors influencing non-uptake in males and females including negative beliefs and emotions related to cancer and screening, poor knowledge and social influences. Additional quantitative analysis of a database of screening invitees provides evidence that increasing male gender and increasing deprivation are independently associated with lower uptake of FIT based screening. In order to test the results of the qualitative study at an aggregate level a survey of users and non-users of an organised FIT-based population-based screening programme confirms that non-use is influenced by negative beliefs and emotions related to cancer and screening, as well as the influence of a partner or spouse. However evidence of gender based differences in the factors influencing uptake of FIT based screening was not found. Further research is required to determine why males are significantly less likely to take part in FIT based screening. More importantly the thesis has begun to identify factors which may be amenable to the development of interventions to improve uptake in Irelands National Colorectal Cancer Screening Programme.

1 Introduction

1.1 Introduction

Colorectal cancer is a major public health problem in Ireland and worldwide. On average 2489 cases of colorectal cancer were diagnosed each year in Ireland during 2012-2014 (1). On average 1018 people died from the disease in Ireland each year during 2011-2013 (1). Colorectal cancer is the second most commonly diagnosed cancer among males (after prostate cancer) and the third most commonly diagnosed among females (after breast and lung cancer). More cases were diagnosed in males (n=1476) compared to females (n=1013) and more male deaths occurred from the disease (594 vs 424) (1). Excluding non-melanoma skin cancer, 10% and 13% of all cancers in males and females respectively are colorectal cancers (1). The age-standardised incidence rate is 63.8 per 100,000 in males and 38.1 per 100,000 in females and, for mortality 26.4 in males and 14.8 per 100,000 in females (1). Colorectal cancer accounts for 13.3% of all cancers in males and 10.4% of all cancers in females.

Natural history of colorectal cancer

Adenomatous polyps and the adenoma-carcinoma sequence

Colorectal cancer occurs in the large bowel which includes the colon and the rectum. Most colorectal cancers develop in the lining of the bowel and often begin as benign non-cancerous tumours known as “adenomas”, “adenomatous polyps” or in some instances “serrated polyps” or “hyperplastic polyps”. The transition from adenomatous polyp to cancerous tumour is known as the adenoma-carcinoma sequence (2,3) while some other sporadic colorectal cancers have been identified through the development of some hyperplastic and serrated polyps (4,5). Most

polyps do not cause severe symptoms and are often excised through the use of colonoscopy (6). About 70% of polyps removed during colonoscopy have been shown to be polypoid adenomas (pre-cancerous lesions which develop through the adenoma-carcinoma sequence) and are known to be responsible for most colorectal cancer development (2,3). It has been reported that the prevalence of colonic adenomas is about 30-40% at 60 years of age, although the lifetime cumulative incidence of colorectal cancer is 5.5% indicating many adenomas of the colon do not progress to cancer (7). However removal of these polyps has the potential to prevent the development of colorectal cancer and this is the basis upon which screening for the disease has been established (8–12).

The transition from polyp to cancerous invasion often takes more than 10 years (3,13,14). Annual transition rates from advanced adenomas to colorectal cancer increase with age (2.6% in females and males between ages 55-59 and 5.6% in females and 5.1% in males in those aged older than 80 years) while 10 year cumulative risk increases from 25.4% (females) and 25.2% (males) at 55 years to 42.9% (females) and 39.7% (males) in those aged over 80 (15).

Incidence from colorectal cancer invasion

The International Association of Cancer Research has reported that colorectal cancer was the third most common cancer in men (746,000 cases) and the second most common in women (614,000 cases) worldwide representing almost 10% of all cancers diagnosed (16). Almost 55% of cases worldwide occur in more developed regions with rates being 10 times greater in the highest regions of incidence of Australia and New Zealand (Age standardised rate (ASR): 44.8 and 32.2 per 100,000

in males and females respectively) to the lowest region of incidence of Western Africa (4.5 and 3.8 per 100,000)(17). However the disparity in incidence in males and females holds across regions (Figure 1) (16). Internationally age-standardised colorectal cancer incidence rates from 1982-1987 through to 1998-2002 increased in males and females in 27 of 51 cancer registries (18). Increases however were primarily in countries in economic transition (Czech Republic & Slovakia, most part of Asia and some South American countries) where rates also increased more prominently in males (18). Rates in more economically developed countries however began to stabilise during the periods 1982-1987 through to 1998-20002 (although the United states observed a decrease in rates) (18). Despite the stabilisation of the rates in longstanding economically developed countries the global incidence of the disease is expected to increase by 79%, mainly due to increasing and ageing populations, although lifestyle factors also play a role (19, 20).

Colorectal cancer survival and disease stage

In 29 European countries with cancer registries average five-year relative survival during the period 2000-2007 was 56.6 (95% CI 56.4-56.76) and Ireland was below this average at 54.3% (95% CI 53.29-55.37) but above countries in the United Kingdom (for instance England 52.08; 95% CI 51.8-52.35) and Eastern European countries (47.3 95% CI 48.0-46.88)(21). Once again as with incidence and mortality, relative survival was generally lower in males across Europe during this period (European average Males: 56.42 (95% CI55.3-56.05); Females 57.66 (95% CI57.4-57.93) and this is also the case in Ireland (Males 52.51 (95% CI 51.08-53.98); Females 56.38 (95% CI 54.88-57.92)(21).

At diagnosis colorectal cancer is staged to determine the extent of the tumour size and if it has spread to lymph nodes and to other parts of the body. Early stage colorectal cancers are referred to as stages I and II and are localised (i.e. have not spread) while stage III has progressed to the lymph nodes and local organs and stage IV to other parts of the body (22). At earlier stages surgery to remove the cancer and nearby lymph nodes is most commonly used, while at later stages the use of chemotherapy, or chemotherapy in conjunction with radiation therapy, is often used and outcomes are poorer as observed in survival rates (23). In the US 5 year relative survival rates for those diagnosed at localised stage are 90%, 69% when spread to lymph nodes or adjacent organs and 12% when spread to distant organs (23). In Ireland, 3 year cancer-specific survival has improved over time and during the period 2006-2009 survival of those diagnosed at stage I was 93% and 83% for those diagnosed at stage II. However 3 year cancer-specific survival at stage III was 67% and 20% for those diagnosed at stage IV (24).

Mortality

Approximately 694,000 deaths occurred from the disease globally, representing 8.5% of all cancer deaths (16). Increasing mortality has been observed in countries within Eastern Europe and in populations in Asia and Latin America (20). 52% of deaths worldwide are in less developed regions with an estimated 175.4 deaths per 100,000 in males and 157.7 deaths per 100,000 in females in more developed regions compared to 198.2 deaths in males and 162.5 deaths in females in less developed regions (16). As with incidence, age standardised mortality rates are generally higher in males (20) (Figure 1). Age-standardised mortality rate decreases have been observed in more developed regions such as the Northern Europe, Canada,

USA, Israel and Australia and New Zealand, and increasing rates have been observed in countries such as China, Croatia, Latvia, Russia Columbia and Costa Rica (20). Overall age-standardised mortality rates are estimated to increase by 85% by 2035 (19,20). The European Standard Population (ESP) mortality rate among males in Ireland was 26.4 per 100,000 and 14.8 per 100,000 in females in the period 2011-2013(1). This represented 12% of all cancer deaths in Ireland (13% in males and 10% in females) in during that period (1).

Risk factors for colorectal cancer

Risk for the development of colorectal cancer can be categorised into modifiable and non-modifiable factors.

Non-modifiable risk factors

Non-modifiable risks are those that an individual has no control over. These include age and hereditary factors. Colorectal cancer is a cancer of older people and 90% of colorectal cancers are diagnosed in those over the age of 50 and incidence is 50 times greater in those aged 60-79 than in those aged less than 40 (25). Other non-modifiable risk factors include a personal history of adenomatous polyps (in the US lifetime risk of developing an adenoma is 19%), a personal history of Inflammatory Bowel Disease (relative risk of developing colorectal cancer is 4-20 fold), a family history of colorectal or adenomatous polyp (up to 20% of those diagnosed with colorectal cancer have family members who have had the disease) or an inherited genetic risk of developing the disease (5-10% of colorectal cancers are hereditary) (25).

Modifiable risk factors

A number of risk factors have been identified which increase the risk of developing colorectal cancer which are modifiable, meaning that the risk develops as a result of environmental factors which people have control over. These include nutritional factors such as the consumption of red meat and high fat diets, lack of physical activity, obesity (in particular abdominal obesity), tobacco use and heavy alcohol consumption (26).

Differences in risk factors in males and females exist and contribute to the excess incidence and mortality of colorectal cancer among males. Smoking rates are almost five times higher in males than females, especially in low and middle income countries, but are somewhat similar in high income countries(27). In Ireland smoking prevalence is 21.6% in males and 17.6% in females. Other risk factors such as overweight and obesity have similar rates in males and females worldwide (37% of males and 38% of females) (28) while in Ireland males are more often overweight (43% of males and 31% of females) with similar rates of obesity in males and females (25% of males and 22% of females) (29). Males also exceed females in their consumption of alcohol, particularly high-volume consumption (30) and this is no different in Ireland (29).

Screening and the adenoma-carcinoma sequence

Colorectal cancer became a focus of screening development because of the establishment of the adenoma-carcinoma sequence and the association between survival and stage of disease. In 1968 the World Health Organisation (WHO) set out 10 principles for the establishment of screening programmes aimed at detecting disease in populations (31). The principles stipulated that:

(1) The condition sought should be an important health problem

(2) There should be an accepted treatment for patients with recognized disease

(3) Facilities for diagnosis and treatment should be available

(4) There should be a recognizable latent or early symptomatic stage

(5) There should be a suitable test or examination

(6) The test should be acceptable to the population

(7) The natural history of the condition, including development from latent to declared disease, should be adequately understood

(8) There should be an agreed policy on whom to treat as patients

(9) The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole

(10) Case-finding should be a continuing process and not a "once and for all" project

The existence of the adenoma-carcinoma sequence and the strong relationship between early stage disease at diagnosis and subsequent improved outcomes provides the rationale for screening. Population-based screening for colorectal cancer involves inviting a defined population who are at average risk of developing the disease to be screened for the disease (32). The aim of such a programme is to identify individuals with the disease at the earliest possible stage or to identify those with pre-cancerous adenomas who are at increased risk of developing colorectal cancer in order to reduce incidence and mortality (32). Population-based screening for colorectal cancer has been present in large parts of Europe for over a decade (33–35). However despite the growth of colorectal cancer screening as an important

public health initiative (36) only a small proportion of the world's population has access to screening (37).

National screening programmes have been established in many countries (34,38,39), on the basis that screening reduces both incidence and mortality through early detection of cancers and/ or detection and removal of adenomatous polyps (10,40–42). Several screening tests exist, including endoscopy-based tests (including flexible sigmoidoscopy and colonoscopy) and faecal tests (such as guaiac-based faecal occult blood Test (gFOBT) and faecal immunochemical tests (FIT)).

Types of screening tests

A number of screening tests exist and these include endoscopic based tests, faecal or blood based tests or computed tomography colonography (CTC). These tests can be divided on the basis of procedurally invasive tests and non-invasive tests. Invasive tests include the use of endoscopic based testing procedures including flexible sigmoidoscopy and colonoscopy, but also the less invasive CTC (also known as virtual colonoscopy) which uses x-ray technology. Non-invasive tests include the use of FOBT and FIT. Research is ongoing in efforts to develop DNA testing, either through blood testing (Blood based DNA methylation or protein markers) (43,44) or stool-based testing (45). However CTC nor the newer DNA based tests have been proven to be cost effective in screening and therefore are not recommended for population based screening (46) although CTC has been recommended in the US as an opportunistic screening test (11). Current screening guidelines in the US recommend screening using invasive procedures every 5-10 years or annually using non-invasive procedures (11), while in Europe only FOBT has been recommended in

population based screening programmes (12). The tests recommended for screening for colorectal cancer are briefly described below.

Endoscopic based tests

Endoscopic based procedures such as colonoscopy and flexible sigmoidoscopy visualise the rectum and colon with the aim of identifying polyps or cancerous neoplasms and are carried out by a medical professional.

Flexible sigmoidoscopy

Flexible sigmoidoscopy involves the insertion of a flexible 60cm long tube into the anus which is advanced slowly into the colon. The procedure allows the practitioner to examine the rectum and sigmoid colon (where approximately two thirds of cancers are located) for abnormalities (47). Flexible sigmoidoscopy can be both a screening tool and a diagnostic tool, and can remove identified adenomas at the time of the procedure. In addition a single screening test can be sufficient to protect against colorectal cancer when offered between the ages of 55 to 64 (42). Screening using flexible sigmoidoscopy has been reported to reduce incidence by 32% and mortality by 50% (48) while meta-analysis of observational studies of colonoscopy have reported a 69% reduction in incidence and a 68% reduction in mortality from the disease (49). A recent Cochrane review indicated a 15% reduction in incidence and mortality when flexible sigmoidoscopy was compared to FOBT screening (50). US guidelines recommend screening using flexible sigmoidoscopy every 5 years (11).

Colonoscopy

Like flexible sigmoidoscopy, colonoscopy also employs the use of a flexible tube (colonoscope) which is inserted into the rectum and colon which allows the practitioner to visually examine the rectum and colon. Colonoscopy has a further advantage over flexible sigmoidoscopy in that it can reach further into the large intestine but is a more onerous procedure on the patient, being associated with higher levels of discomfort and complication rates (49). Colonoscopy is the diagnostic procedure within most screening programmes but is often the screening test of choice in US based opportunistic screening (51). In the absence of randomised control trials (which are underway but will take another decade to report results) a recent systematic review of observational studies reported a 61% reduction in the relative risk of incidence and mortality from colorectal cancer while in subgroup analysis of screening colonoscopy incidence there was an 89% reduction in incidence (52). US guidelines recommend screening using colonoscopy every 10 years (11).

Faecal based tests

Adenomas are often asymptomatic but can produce blood in the stools, which may go undetected. Faecal based tests (FOBT, FIT and faecal DNA tests) aim to detect non-visible traces of blood in the faeces which can be a marker of upper or lower gastrointestinal bleeding as a result of adenomatous polyps or carcinomas. If blood is detected a recommendation for diagnostic testing using colonoscopy (or CTC if the individual is unsuitable for colonoscopy) will be made. As described above, faecal DNA test are not used within organised screening programmes due to a lack of evidence on cost-effectiveness(46). Currently two types of faecal test are available

which are used within organised population-based screening programmes, gFOBT and FIT.

gFOBT

The gFOBT test aims to detect blood in the stool through a reaction with guaiac (contained in the test) and the enzyme peroxidase (found in blood) (53). The test can be carried out at home and can be return to a laboratory via the postal system (38). For a successful test to be completed a 3 samples on consecutive days are usually required (54,55), using a sampler and placing the samples on a card (38). Laboratory results indicate if the sample is positive or negative for blood. However the reaction between guaiac and peroxidase may detect blood which does not originate in the colon or rectum, or non-human blood from red meat (as well as some raw plant foods) (53). For this reason, dietary and medicinal restrictions are required before completing the test. Reviews have reported reductions in mortality of between 15-33% compared with no screening (41,56). In the European Union it is recommended the test be carried out biennially in population based screening programmes (12) while in the US annual opportunistic screening is recommended using gFOBT.

FIT

The FIT also detects blood in the faeces but unlike gFOBT it is specific to human blood. The test works through the reaction of antibodies specific for human haemoglobin with blood (53,57,58) and is more selective for blood originating in the colon and rectum compared to the gFOBT. The test can be carried out at home and requires either one sample or two samples on consecutive days depending on the sensitivity threshold set (59). Completed tests are sent via post to a laboratory for analysis. A positive result requires follow-up diagnostic colonoscopy (11,13).

Unlike FOBT, dietary and medicinal restriction are not required and this makes the test easier and more acceptable to screening populations while reducing the number of false positive results that may occur in gFOBT based screening (53). An additional advantage of FIT is that the test is quantitative and therefore the processing and reading of the test can be automated, and standard cut off values of haemoglobin detection can be set to a positivity rate that meets the capacity of colonoscopy resources available within screening programmes (60).

Some evidence indicates FIT is a cost-effective alternative to gFOBT (reviewed in (12)), and more recently has been shown to outperform gFOBT with almost double the sensitivity in detecting advanced neoplasia (61). FIT has not been shown to reduce incidence or mortality as randomised control trials of have not been carried out. However Allison et al have argued that this is not necessary as FIT has demonstrated superior performance characteristics as described above and boasts a significant enhancement on the detection of occult faecal blood in faeces in subjects most likely to harbour advanced neoplasia (62). Screening using FIT is recommended annually in the US (11) or every two years in EU (12).

Organised population-based screening

At this point it has been established that screening for colorectal cancer has been shown to reduce incidence and mortality from the disease (13,41,42,56,58). High uptake in screening is vital in maximising the benefits to the population through reductions in incidence (by preventing the disease from occurring) and mortality (by detecting the disease at earlier stages) (12,63). Faecal-based tests, notably gFOBT,

are generally the route through which organised population-based colorectal cancer screening programmes are being delivered internationally (34). Uptake rates have been shown to be lower when using colonoscopy or sigmoidoscopy as the initial screening test (64), while uptake has been shown to be higher with the use of FIT compared to gFOBT (65). In addition Significant differences in screening uptake by gender have also been reported in the UK and US with females more likely to take part in screening when g-FOBT is offered as the initial screening test (66,67). Deprivation has also been reported in the UK gFOBT screening programme with 35% uptake in the most deprived areas compared to 61% in the most affluent areas (66). The deprivation gradient was steeper in females than males indicating better uptake in females as affluence increases (66). These findings on uptake by gender and deprivation are limited to g-FOBT screening, and no data is available on these factors in FIT based screening, which will be a focus of this thesis.

Screening sigmoidoscopy and screening colonoscopy have been shown to prevent the majority of deaths from distal colorectal cancer, while screening colonoscopy can prevent deaths from proximal colon cancer (5,49). However risk reduction may vary according to factors such as the quality of endoscopy, age at screening or risk factor profiles (including genetic factors)(13). When compared to FIT, Colonoscopy has shown to have significantly higher rates of detection of advanced adenomas, advanced neoplasia and non-advanced adenomas, but similar detection rates of cancer (68). Alison et al has concluded that FIT has higher sensitivity and specificity for distal colon cancer when compared to gFOBT (62).

Higher proportions of females and older people present with right-sided colon cancers and these cancers are often at a more advanced stage at diagnosis and have a higher mortality risk (69,70), although recently it has been suggested that the

prognosis of those diagnosed with right sided colon cancers at stages I-III is better compared to those diagnosed with left-sided colon cancers (71).

Major sex differences have also been reported in the performance of gFOBT and FIT, with the detection of advanced neoplasia higher in males and corresponding lower sensitivity in males compared to females (72).

Colorectal cancer screening in Ireland

In 2007 the National Cancer Screening Service (NCSS now the National Screening Service (NSS)) board established an expert advisory group to examine the scientific evidence related to screening for colorectal cancer in Ireland. The group recommended that the FIT operating on an automated platform should be the primary screening tool for a population-based colorectal cancer screening programme in Ireland. It further went on to state that this would be the first international colorectal cancer screening programme utilising this technology as a primary screening tool (73).

The NSS commissioned the Health Information and Quality Authority (HIQA) under the advice of an expert advisory group to undertake a Health Technology Assessment (HTA) of the relative cost effectiveness of various options for a population-based colorectal cancer screening programme in Ireland compared to no programme and this was carried out and published in 2009 (32). The HTA also estimated the resource requirements (in terms of colonoscopy capacity) and potential health outcomes (number of cases of adenomas and cancers detected) that could result in the first decade following implementation of a screening programme. The HTA examined a number of options for the initial screening test for population-based screening in Ireland. This was guided by the volume and strength of available

scientific evidence, knowledge of screening practices in other countries and consideration of the acceptability, feasibility and risk of serious adverse events as a result of screening (32). Three main screening scenarios were established by the expert advisory group:

- Biennial gFOBT, with reflex FIT testing, in those aged 55-74 years;
- Biennial FIT, in those aged 55-74 years;
- Once-only flexible sigmoidoscopy, at age 60.

Based on available evidence obtained from literature review it was assumed uptake of FIT and gFOBT would be 53% and 39% using once-only flexible sigmoidoscopy, Therefore in year one of a programme it was assumed that 189,640 completed kits would be returned using gFOBT or FIT (based on a screening age range of 55-74), while 18,617 individuals would undergo screening using flexible sigmoidoscopy. Given demographic changes in the population and assuming uptake remains constant the number screened by gFOBT or FIT would increase by 16-17% and by 11% using flexible sigmoidoscopy (32).

The HTA team reported that all three options were likely to be cost effective in terms of the threshold set (historical, notional, cost effectiveness threshold of €45,000 per Quality Adjusted Life Year (QALY))(32). The results of the HTA cost-effectiveness analysis showed that a screening programme based on FIT would cost more than programmes based on gFOBT or flexible sigmoidoscopy, however FIT screening would provide the greatest health gain (QALYs or Life years gained (LYG)) compared to a policy of no screening, while remaining highly cost effective relative to other screening options, (32). Compared to no screening the following incremental

cost-effectiveness ratios (ICERs) were obtained for the three core screening scenarios:

- Biennial FIT (55 to 74 years): €1,696/QALY
- Biennial gFOBT (55 to 74 years): €4,428/QALY
- Once-off FSIG at age 60 years: €589/QALY.

HIQA recommended a biennial FIT based colorectal cancer screening programme with an age range of 55-74 as the one which would provide the greatest health gain to the population and would also result in:

- The highest estimated lifetime reduction in the incidence (14.7%) and mortality (36.0%) from colorectal cancer
- The highest percentage of lifetime cases of screen or surveillance-detected cancers (31.6% of all cancers versus 13.8% for gFOBT and 3.3% for flexible sigmoidoscopy) and adenomas.

The authors also suggested that because screen-detected cancers are more likely to be detected at an earlier stage (stage I or II) than those detected symptomatically survival rates would also improve. HIQA was further requested by the Minister for Health and Children to undertake an evaluation (74) aimed at:

- identifying the resources assigned colonoscopy services within the hospital system and assess the potential to apply or build upon these resources effectively within a national colorectal cancer screening programme
- advising on a model for a national colorectal cancer screening programme, including options for phased implementation as set out in the HTA of a population-based colorectal cancer screening programme in Ireland

- advising how the national colorectal cancer screening programme can be run effectively in a quality assured manner within the existing resources available to the NCSS and the Health Service Executive (HSE)
- examining potential synergies between the current and proposed population-based cancer screening programmes with a view to maximising and optimising efficiencies

The HIQA evaluation recommended a cost effective model for the delivery of colorectal cancer screening which would build upon existing capacity within the health system utilising a number of cost savings and efficiencies, identified within the evaluation (74). The key elements of a national screening programme included (74):

- 8-12 symptomatic services delivering colonoscopies generated from the screening programme which would be centres based within hospitals with those hospitals deciding upon the most effective solution matching their available facilities, resources and staff
- Use of advanced nurse practitioners in the delivery of the service
- Appropriate diagnostic and treatment pathways be put in place for other procedures (CTC or surgery)
- Gap analysis to determine additional need for consultant radiologist, radiographer or specialised equipment
- Development of a national quality assurance programme
- the principles of good client care established within the breast screening programme should also be encompassed within this screening model
- Operation of a multidisciplinary team approach with the screening programme

- Laboratories utilised for histology should have appropriate internal quality control and external quality assurance

The next steps in the implementation of FIT based colorectal cancer screening was presented in 2010 (75) and was based on the findings of the HIQA HTA and evaluation outlined above (32,74).

Prior to the HTA only a two studies of colorectal cancer screening existed in Ireland. The first was a program inviting construction workers to take part in screening with either gFOBT or FIT tests (76). Following from this a pilot screening programme was established in an area in Dublin. The Adelaide and Meath Hospital / Trinity College Dublin Colorectal Cancer Screening Programme (TTC-CRC-SP) was Ireland's first population-based two-step (two FIT samples required on consecutive days) colorectal cancer screening programme and ran over two rounds during 2008-2010 and 2011 to 2012 (77–79). Uptake in Round 1 was 51% and was slightly lower in round 2 at 47.5% (79). This programme provided valuable evidence on the potential success of implementing FIT based colorectal cancer screening in the population at large.

The roll-out of a national population-based colorectal cancer screening programme in Ireland began in December, 2012 – the first national programme to be based on primary FIT (73). Initially, individuals aged 60-69 are invited for biennial screening with FIT, with follow-up of positive test results by diagnostic colonoscopy at one of twelve centres associated with the screening programme. While some evidence exists in terms of factors influencing uptake of colorectal cancer screening, very little

evidence exists in relation to FIT based screening specifically. In addition, very little is known about whether males are more or less likely to take part in screening, especially in light of their higher risk of developing and dying from the disease.

Conception of this PhD

This study was conceived after the author attended a conference on men's health in 2010 in which the then Irish minister for health gave the closing speech. The minister discussed the development of the national colorectal cancer screening programme and that this would be the first organised cancer screening programme available to men (Ireland having had breast cancer screening since 2000 and cervical cancer screening introduced the previous year in 2009). At the time, in collaboration with the National Cancer Registry Ireland (NCRI), the author, working for the Centre for Men's Health, was conducting a study on the excess burden of cancer in men in Ireland. That study reported significantly higher rates incidence and mortality of five of the leading non-sex specific cancers (lung, colorectal, bladder, stomach and melanoma skin cancer) in males (80). The imminent implementation of colorectal cancer screening in Ireland, and the fact that males had significantly higher incidence and mortality from colorectal cancer, was the germ for the development of a PhD proposal aiming to investigate FIT-based colorectal cancer screening in males and females. The fact that this would be the first time men in Ireland would be offered the opportunity to be screened for cancer added value and relevance to the proposal. The author was successful in securing funding through an Irish Cancer Society scholarship.

1.2 PhD aims and objectives

The objectives of this PhD project were:

Aim:

The overall aim of this PhD project was to describe uptake in FIT based colorectal cancer screening and to explore the impact of gender on uptake.

The specific objectives (Figure 1.2) were to:

1. Describe the burden of colorectal cancer in Ireland (chapter 2)
2. Review uptake in FIT-based colorectal cancer screening in males and females internationally (Chapter 3)
3. Identify factors associated with use and non-use of FIT-based colorectal cancer screening in males and females including any differences and factors associated with these differences (Chapter 4 & 6)
4. Explore specific barriers, motivators and facilitators associated with FIT-based colorectal cancer screening in males and females (Chapters 5 & 6)
5. Inform future roll-out of colorectal cancer screening in Ireland (Chapter 7)

1.3 Thesis Outline

Chapter 2 of the thesis is a descriptive epidemiological study of colorectal cancer in Ireland from 1994 to 2010 using NCRI data. This chapter describes the overall patterns of colon and rectal cancer in males and females and describes incidence, mortality and survival from the disease prior to the introduction of national population based screening.

Chapter 3 describes a systematic review and meta-analysis of FIT based screening uptake in males and females internationally. The analysis also investigated factors

associated with uptake as they pertain to study design and organisation of screening programmes.

Chapter 4 reports a qualitative study nested within a population-based FIT-based colorectal cancer screening programme which explored factors associated with uptake in male and female users and non-users. The Theoretical Domains Framework (TDF) was employed to provide a theoretical framework for the study and to make sense of individual's discourse on influences on their decisions about whether or not to participate in FIT based screening.

Chapter 5 is a quantitative study, utilising the database of a population based FIT-based colorectal cancer screening programme, investigating uptake in relation to sex, deprivation status and age.

Chapter 6 describes the final phase of the overall study, again nested with the population based screening programme, and is a cross-sectional survey of male and female users and non-users of the screening programme. The study investigates some of the factors identified in the qualitative phase (described in chapter 4) in a population-based sample of FIT screening users and non-users and moves towards the identification of behaviours which may be amenable to the development of interventions to improve uptake in Ireland's national colorectal cancer screening programme.

Chapter 7 is a discussion and final conclusion drawing together the evidence base established in the study, and presents implications for Irelands national screening programme and potential avenues for future research.

Contributors to the work of this thesis

In chapter 2 Dr Joseph McDevitt carried out the statistical analysis of data presented in this paper. Data was drawn from the National Cancer Registry. In chapter 3 Dr Aoife Osborne acted as second reviewer for the completion of the systematic review. In chapter 4 invitations to potential participants was managed by Claire O'Callaghan in the National Cancer Registry. Interview recordings were transcribed by a third party, Devon Transcription Ltd. Dr Mairead O'Connor double coded a number of transcripts to ensure rigour in the process of analysis. Prof Pamela Gallagher provided advice and support in use of the Theoretical Domains Framework and provided feedback of drafts of chapters 4 and 7. In chapter 5 the TTC-CRC-SP database was geo-coded by Mr Neil McCluskey of the National Cancer Registry and Dr Katie O'Brien provided statistical advice in its analysis. For chapter 6 the cross-sectional postal survey invitations and access database was managed by Ms Claire O'Callaghan. Ms O'Callaghan also managed the packaging of invitations and data entry for the survey. Further support in delivery and data entry of the survey was provided by research assistant Ms Antonia Virovska. Professor Linda Sharp and Professor Patricia Kearney supervised the entire PhD.

Candidate's contribution

For the population based epidemiological study (chapter 2) the PhD candidate, Nicholas Clarke, lead on the write up of the data and submitted and defended the

manuscript throughout the journals peer review process. The candidate carried out all literature reviews, systematic review data collection and analysis including meta-analysis (Rev-Man) described in Chapter 3. The candidate managed the population based screening database described in Chapter 4 and carried out all analysis. For the qualitative study (Chapter 5) the candidate was responsible for the design of the topic guide, recruitment of participants, conducted all interviews (N=50) and carried out all analysis (managed in NVivo software). The candidate designed the questionnaire and managed the database of invitees for the survey in Chapter 6. The candidate also jointly managed the recruitment and delivery of the postal questionnaire and reminders to the 7500 individuals invited to participate. All data cleaning was carried out by the candidate. All statistical analysis was carried out by the candidate using STATA 14 (except in the case of chapter two as described above). The candidate led on the write up of all five studies and the submission and defence of the each study throughout the peer review process within each journal.

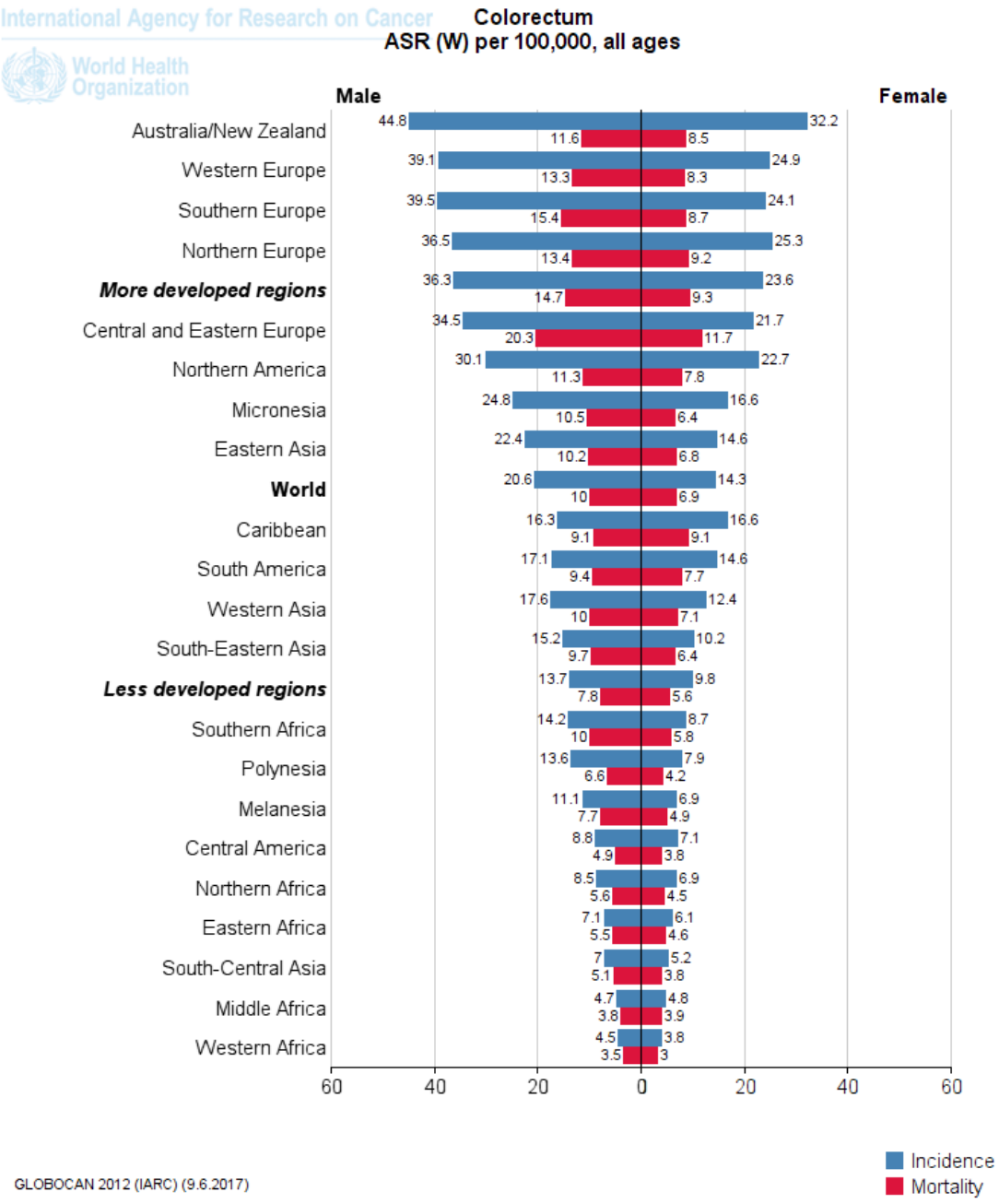

Figure1.1: World age-standardised incidence and mortality rates of colorectal cancer by sex and population

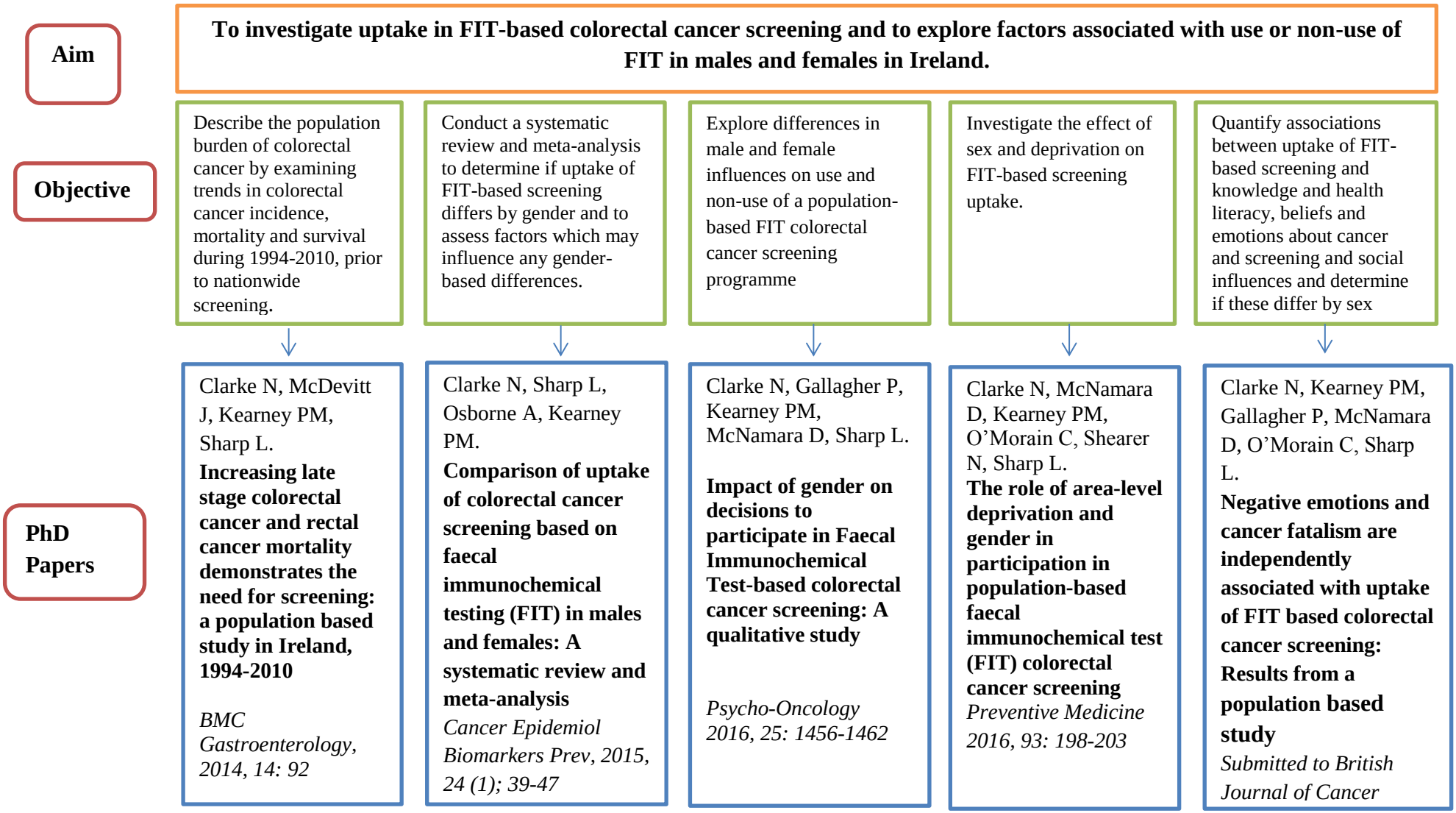

Figure 1.2: Aims and objectives and overview of thesis

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2 Increasing late stage colorectal cancer and rectal cancer mortality demonstrates the need for screening: a population based study in Ireland, 1994-2010

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2.1 Abstract

Background: This paper describes trends in colorectal cancer incidence, survival and mortality from 1994 to 2010 in Ireland prior to the introduction of population-based screening.

Methods: We examined incidence (National Cancer Registry Ireland (NCRI) and mortality (Central Statistics Office) from 1994 to 2010. Age standardised rates (ASR) for incidence and mortality have been calculated, weighted by the European standard population. Annual percentage change was calculated in addition to testing for linear trends in treatment and case fraction of early and late stage disease. Relative survival was calculated considering deaths from all causes.

Results: The colorectal cancer ASR was 63.7 per 100,000 in males and 38.7 per 100,000 in females in 2010. There was little change in the ASR over time in either sex, or when colon and rectal cancers were considered separately; however the number of incident cancers increased significantly during 1994-2010 (1752 to 2298). The case fractions of late stage (III/IV) colon and rectal cancers rose significantly over time. One and 5 year relative survival improved for both sexes between the periods 1994-2008. Colorectal cancer mortality ASRs decreased annually from 1994-2009 by 1.8% (95% CI -2.2, -1.4). Rectal cancer mortality ASRs rose annually by 2.4% (95% CI 1.1, 3.6) and 2.8% (95% CI 1.2, 4.4) in males and females respectively.

Conclusions: Increases in late-stage disease and rectal cancer mortality demonstrate an urgent need for colorectal cancer screening. However, the narrow age range at which screening is initially being rolled-out in Ireland means that the full potential for reductions in late-stage cancers and incidence and mortality are unlikely to be

achieved. While it is possible that the observed increase in rectal cancer mortality may be partly an artefact of cause of death misclassification, it could also be explained by variations in treatment and adherence to best practice guidelines; further investigation is warranted.

2.2 Introduction

Over 1.23 million colorectal cancers are diagnosed worldwide annually with 609 000 deaths(1). Colorectal cancer is highly preventable if diagnosed early and treated. Screening has been available for many years through several modalities, including colonoscopy, sigmoidoscopy, and faecal-based tests (2–4). Faecal-based tests, notably gFOBT, are generally the route through which colorectal cancer screening programmes are being delivered internationally (5,6). More recently FIT has been recommended for screening due to its improved sensitivity and specificity in detecting human haemoglobin and the fact that there is no need for test recipients to undergo dietary restrictions (which may be required for guaiac-based tests). Studies which have used FIT suggest improved uptake compared to other screening tests such as FOBT, possibly due to the absence of dietary restrictions, the need for fewer samples, absence of the need for storage if a one sample test, and ease of use (7). However the authors state that these results are inconclusive and require further investigation from the patient's perspective (7). Recent European and US guidelines recommend FIT as the initial screening test in population-based screening programmes (8,9).

Screening aims to detect colorectal disease either at a precancerous stage (when removal of polyps may prevent cancers developing) or when cancers are at an early stage (when treatment is more effective and patients may also benefit from improved quality-of-life). Screening therefore has the potential to reduce mortality, provided the services is high quality and coverage is high (8).

Although many European countries have established screening programmes, until 2013, no programme was in place in Ireland. In 2009, a health technology

assessment of population-based colorectal cancer screening found that biennial FIT at ages 55-74 would be considered the optimal screening strategy in Ireland in terms of potential for reducing incidence and mortality, and cost-effectiveness (10). The NCSS launched BowelScreen, a national population-based programme, in December 2012. This paper aims to describe the population burden of colorectal cancer by examining trends in colorectal cancer incidence, mortality and survival during 1994-2010, prior to nationwide screening.

2.3 Methods

We examined incidence for 1994-2010 and mortality for 1994-2009 (2009 was the latest year for which mortality data was available at the time of the study). Information on incident cases was abstracted from the NCRI. The NCRI records all cancers diagnosed in the population usually resident in Ireland through active case finding by tumour registration officers. The completeness of registration for all invasive cancers diagnosed to end 2008 was estimated to be over 97% (11).

The NCRI has permission under the Health (Provision of Information) Act 1997 to collect and hold data on all persons diagnosed with cancer in Ireland. The use of that data for research is covered by the Statutory Instrument which established the Registry Board in 1991 All datasets were anonymised prior to analysis.

Site of tumour was recorded according to the International Classification of Diseases 10th revision (ICD10), and analysis included all primary invasive cancers of the colon (C18) and rectum (C19-C20) with a date of diagnosis during 01/01/1994 and 31/12/2010. For each diagnosed cancer, summary stage was derived from primary tumour (T), regional nodes (N) and distant metastasis (M) as recorded in pathology

reports or, in the absence of these, from clinical staging, according to TNM 5th edition (12). Where a patient was classified as MX ("distant metastases cannot be assessed"), the M category was defaulted to "M0" (no distant metastasis). For example, a patient with stage composite T3N1MX was treated as T3N1M0, stage III (Dukes C). Data on treatment received during the first year post-diagnosis was defined as planned first course of tumour directed treatment administered within one year of the diagnosis date (-30 to 365 days) and aimed at removing, destroying or preventing further tumour growth and included four treatment scenarios: (Surgery (Y/N), chemotherapy(Y/N), radiotherapy(Y/N), or not treated [ICD9CM and ICD10-AM]). Analyses of stage and treatment included cases diagnosed 1995-2009, as this information was incomplete for 2010 cases and unreliable for 1994 cases, the first year of national registration. Colorectal cancer deaths (C18-20) were obtained from the Central Statistics Office (CSO) (13).

Age-standardised rates (ASR) for incidence and mortality were weighted by the European standard population using the direct method (14). Trends presented as annual percentage change (APC) in ASRs of incidence (1994-2010) and mortality (1994-2009) were calculated using Joinpoint regression (15). Joinpoint regression was also used to test for linear trends in treatment (1995-2009) and case fraction of early (stage I/II) and late (stage III/IV) disease (1995-2009). For descriptive purposes, age category percentages and treatment category percentages were given for three diagnostic periods: 1995-1999, 2000-2004 and 2005-2009.

In the Irish cancer registry, follow-up of cases is passive, where registered cancer cases are linked to death certificates provided by the Central Statistics Office (CSO) (16). For survival analysis, the dataset was divided into three diagnostic periods:

1994-1998, 1999-2003 and 2004-2008. Survival time was censored at 31 December 2009 to ensure all cases had at least one year follow-up, and because this was the latest date for which death ascertainment was complete. Our manuscript was drafted in late 2013, a point in time when we were confident that all deaths certificates from the CSO were matched to the cancer registry database. Cases which were preceded by another cancer (other than non-melanoma skin cancer) were excluded from survival analysis as were autopsy-only cases, death certificate only cases (DCO), colorectal cancers concurrent with other invasive malignancy and colorectal cancers diagnosed 2009-2010. Relative Survival (RS), the ratio of observed survival among a group of cases to the expected survival among the general population of the same age, sex and country, was computed based on deaths from all causes and using national life-tables (17).

2.4 Results

Incidence

The colorectal cancer ASR was 63.7 per 100,000 in males and 38.7 per 100,000 in females in 2010. There was little change in the ASR over time (Figure 2.1) in either sex, or when colon and rectal cancers were considered separately. However, the number of colorectal cancer cases in Ireland increased from 1752 in 1994 to 2298 in 2010, an annual rise of 2.1% (95% confidence interval (CI) 1.8, 2.4; $p < 0.001$). The increase was somewhat higher in males (983 in 1994; 1343 in 2010; APC = 2.3%, 95% CI 2.0, 2.7) than females (769 in 1994; 955 in 2010; APC = 1.8%, 95% CI 1.4, 2.1).

In males, 62% of cases were in the colon; this was 71% in females. Increases in cases were observed in both colon (APC males = 2.6%, 95% CI 2.0, 3.2; APC females = 1.8%, 95% CI 1.4, 2.3) and rectal cancer (APC males = 1.9%, 95% CI 1.0, 2.4; APC females = 1.7%, 95% CI 1.4, 2.5).

Age distribution

69% of cases in males and 67% in females occurred in those aged ≥65; similar proportions in each sex were diagnosed aged 55-64 (males: 20%; females: 19%) and <55 (males: 11%; females: 14%). Over the three periods 1995-1999, 2000-2004 and 2005-2009 there was no change in the age distribution of either colon or rectal cancer in females or rectal cancer in males (data not shown).

Stage

During 1995-2009 early stage (I/II) colon cancers decreased by -1% annually in males (95%CI -1.8%, -0.1%) and in females by -0.7% (95% CI -1.4%, -0.1%). Conversely late stage (III/IV) colon cancers increased by 1.3% in males (95% CI 0.6%, 2.1%) and by 1.6% in females (95% CI 0.9%, 2.3%). Similarly early stage rectal cancers decreased by -2.1% (95% CI -2.8%, -1.4%) in males and -1.8% (95% CI -2.9%, -0.7%) in females, while late stage disease increased significantly (males: APC = 2.0%, 95% CI 1.2%, 2.7%; females: APC = 1.8%, 95% CI 0.7%, 2.8%; Figure 2.2). Unstaged colon cancers decreased significantly in males by -2.2% (95% CI -4.1%, -0.2%; p-trend <0.05) and by -3.3% in females (95%CI -5.7%, -1.0%; p-trend < 0.05) annually. There was no significant change in unstaged rectal cancers in males (APC 0.6%, 95% CI -2.3%, 1.2%; p-trend = 0.5) or females (APC = 0.2%, 95% CI-2.3%, 2.8; p-trend = 0.8).

Treatment

Use of cancer-directed surgery (i.e. resection) for colon cancer increased from 76% in 2009 to 79% in 2009 (APC 0.3%, 95%CI 0.0, 0.6; p = 0.027), while for rectal cancer there was little change, remaining at 74% over the same period (APC -0.1%, 95%CI -0.5, 0.3; p = 0.54) (Figure 2.3). Use of chemotherapy for colon cancer rose significant from 21% in 1995 to 40% in 2006, thereafter levelling off to 38% up to 2009(APC = 5.7%, 95%CI 4.3, 7.1; p < 0.001). Similarly, in rectal cancer, chemotherapy use increased significantly from 22% in 1995 to 48% in 2002 (APC = 11.1%, 95%CI 8.7, 13.5; p < 0.001), reaching 49% by 2009 (Figure 2.3). Use of radiotherapy for rectal cancer increased significantly from 18% in 1995 to 37% in 2001, thereafter levelling off to just under 40% (APC 12.3%, 95% CI 9.1, 15.7; p < 0.001). The proportion of rectal cancer patients who received pre-surgery radiotherapy increased from 2% in 1995 to 13% in 2002 (APC 38.7%, 95% CI 28.7, 49.5; p < 0.001). Thereafter, the proportion receiving this combination increased at a slower rate from 18% in 2003 to 26% in 2009 (APC 9.9%, 95% CI 1.9, 18.4; p = 0.02) (Figure 2.3).

Survival

Relative survival improved over time for both sexes for colon and rectal tumours. From 1994-1998 to 2004-2008 1-year colon cancer survival in males increased by 8 percentage points to 77% (95% CI 75%, 78%), and in females by 5 percentage points to 73% (95% CI 71%, 75%). Five-year colon cancer survival increased by 8 percentage points to 58% (95% CI 56%, 61%) in males and by 7 percentage points to 59% (95% CI 56%, 62%) in females over the same time (Figure 2.4). One-year rectal cancer survival improved in males by 9 percentage points to 81% (95% CI

79%, 82%) and in females by 6 percentage points to 80% (95% CI 78%, 83%); 5-year rectal cancer survival in males improved by 9 percentage points to 55% (95% CI 52%, 59%) and in females by 9 percentage points to 61% (95% CI 57%, 65%; Figure 2.5).

Mortality

In 2005-2009, on average 400 females (255 colon; 145 rectum) and 552 males (313 colon; 239 rectum) died from colorectal cancer annually. Colon cancer deaths declined over time in both sexes (males: 360 in 1994; 302 in 2009; APC = -1.7%, 95% CI -2.4%, -1.0%; females: 321 in 1994; 240 in 2009; APC = -2.1%, 95% CI -3.0%, -1.2%). Rectal cancer deaths rose significantly in males from 148 in 1994 to 262 in 2009 (APC = 4.6%, 95% CI 3.4%, 5.9%) and in females from 94 in 1994 to 141 in 2002 (APC = 4.4%, 95% CI 3.0%, 5.9%).

Colorectal cancer age-standardised mortality rates (ASR) decreased by -1.8% (95% CI -2.2%, -1.4%) annually during 1994-2009. Colon cancer ASRs fell in both sexes (males: APC = -3.7%, 95% CI 4.4%, -3.0%; females: APC = -4.2%, 95% CI -5.1%, -3.2%), but rectal cancer ASR (mortality) rose (males: APC = 2.4%, 95% CI 1.1%, 3.6%; females: APC = 2.8%, 95% CI 1.2%, 4.4%; Figure 2.6).

2.5 Discussion

Over the past 20 years the number cases of colorectal cancer has increased significantly in Ireland; however once adjusted for changes in the age distribution of the population over time the rate has remained stable. Internationally colorectal cancer rates have stabilised in economically developed countries and Ireland is no exception in this regard (18). In comparison to other European countries, in 2008

Ireland had a higher incidence rate than the EU average and 23% higher than the rate in the United Kingdom (19). In the European region incidence has increased in males at a greater rate than female incidence during the period 1988 to 2008 (20). Survival was just below the EU average but similar to the United Kingdom (21). The improvements in survival reported in this paper were also seen in other European countries during the 1990s and early 2000s (21). European 5 year survival of colon cancer increased from 54.2% in the period 1999-2001 to 58.1% in 2005-2007, and from 52.1% to 57.6% for rectal cancer over the same period (22). Although Irish survival improved, it is still lower than the European average (22). Our data indicates that survival continued to improve for cases diagnosed during 2005-2009. While we did not have detailed information on the dose and intensity of chemotherapy and radiotherapy regimens, better uptake in and application of treatment options during 1995-2009 correlate with the improvement in survival.

Stage

One of the striking findings of this study was that almost half of cases had relatively late stage at diagnosis (stage III/IV) and, over the period under investigation, the proportion with stage III/IV disease increased from 42% to 50%. The increase in stage III/IV cancers is likely to be as a result of more comprehensive investigation in the peri-operative period, with improvements in imaging and diagnostic methods, resulting in a significant shift in stage allocation from stage I/II to stage III/IV over the years 1995-2009. Another possibility is that the number of nodes taken at resection increased over the period 1995-2009, thereby leading to a situation where the probability of finding a positive node(s) increased commensurately, which would have tipped the balance in favour of stage III/IV over stage I/II according to UICC-

TNM, 5th edition. However, we do not have details on node count to support this hypothesis. This question will be addressed in a more comprehensive study of stage migration in colorectal cancer at this registry.

If effective, screening has the potential to change the stage distribution of colorectal cancer in the population. As regards FIT-based screening, which is being implemented in Ireland, Cole et al reported that colorectal cancers were detected at significantly earlier stages in those invited to participate in a screening programme using FIT (23). In a health technology assessment for Ireland, it was estimated that, by year 10 of a programme, the percentage of cases diagnosed at stages I/II would increase from 46% to 53% and stages III/IV decrease from 54% to 47% (10). These estimates were based on screening targeted at those aged 55-74 with a best case scenario uptake of 53% (based on the UK experience of FOBT screening) (24). Similar uptake has been achieved in pilot FIT screening in Ireland (25). The BowelScreen programme, which has recently commenced, is initially inviting individuals aged 60-69. While the stated intention is to eventually include 55-74 year olds, this is likely to take a number of years due to the development of colonoscopy capacity. Therefore the estimates of potential reductions in late stage disease are very unlikely to be achieved by year 10 of the programme.

Mortality

In 2008 Ireland ranked midway of 30 European countries in relation to mortality, similar to the EU average but marginally higher than the United Kingdom (19). Annual decreases in age standardised mortality rates for colorectal cancer in males and females were observed in this study. However this concealed significant increases in the mortality rate for rectal cancers of 2.4% in males and 2.8% in

females. Scrutiny of European data reveals that most countries have experienced static mortality rates over the past 15-20 years. However a few, in addition to Ireland, have described increases. These include Spain, with an APC of 3.5% during 1994-2005, Malta with an APC of 5.2% during 1994-2008 and among selected registries in Germany with an APC of 17.1% during 1998-2007 (26). In terms of potential explanations for these trends, the first that must be considered is whether it might be an artefact of coding of rectal cancer deaths. We have shown that there was a significant decline in the annual death rate for pooled colorectal sites. Yet, there was a steeper decline in the rate of colon deaths, with a compensatory increase in the rate for 'rectum' deaths. This suggests that there may have been a subtle shift in death certificate coding allocation from 'colon' to 'rectum' over the period we have examined. It has long been recognised that physicians tend to report non-specific cancer sites on death certificates; thus, if physicians change how they record cause of death on the death certificate over time, this may induce an apparent change in mortality rates (27). In 1981, Percy et al reported that misclassification led to over reporting of colon cancer deaths and underreporting of rectal cancer deaths (27). More recently, in the US, Yin et al reported inaccurate coding of underlying cause of death, with the vast majority of misclassifications being colon cancers incorrectly classified as rectal cancers (28). Further investigation is warranted to explore the extent and nature of misclassification on death certificates in European countries in recent years, perhaps comparing countries with rising and static rectal cancer mortality rates.

Another possible explanation of the observed increase in rectal cancer mortality is patterns in treatment utilisation. Pre-operative radiotherapy has been recommended for resectable rectal cancer in recent years (29,30) and in line with this the

proportion who received pre-operative radiotherapy has increased markedly since 2000, in Ireland and in other countries (31). However Carsin et al have reported low use of radiotherapy in Ireland (27%) (31) compared to US and EU populations (46%-62%) (32–34). Moreover, although data from trials suggests that pre-operative use is more effective, a significant proportion treated with radiotherapy in Ireland receive it post-operatively rather than pre-operatively (31). These observations raise the possibility that underuse of radiotherapy, particularly preoperative radiotherapy, may be a contributor to rectal cancer mortality trends. Moreover, while the current study found that radiotherapy use was continuing to rise, any impact of this on mortality rates will not be seen for several years.

In terms of surgery, evidence-based guidelines have been published in Ireland aimed at standardising surgical management of rectal cancer (30). An audit of all rectal cancers diagnosed in 2007 found that, while guidelines were in place, best practice was frequently not adhered to (35). Surgery for rectal cancer can result in significant morbidity if undertaken without appropriate and accurate pre-operative staging. Accurate localisation of the tumour (36–38), use of MRI (magnetic resonance imaging) (39) and ERUS (Endo-rectal ultrasound) (40–42) as diagnostic tools, and recording of accurate pre-operative histological data (43,44), are all essential for successful treatment. However the national audit revealed that there were often inadequate investigations and/or recording of such data (35). In addition while multi-disciplinary meetings (MDM) have been shown to improve outcomes for rectal cancer (45,46), treatment options were only discussed at MDMs for around half of patients. Moreover patients treated at low volume centres were less likely to be discussed at MDMs and to have neo-adjuvant therapy (35). Further evidence suggests that comorbidity, rather than age, in elderly rectal cancer patients increases

risk of death after surgery (47). Therefore age alone should not dictate the use of restorative rectal resection (47). However, our analyses indicate lower use of surgery in elderly than younger patients (≥75; 81%; <75: 92-99%) as well as larger increases in age standardised mortality in those aged 70 and older (13). These observations, combined with likely under use of best practice, may provide a possible explanation for the observed trends in mortality.

Biennial FIT-based screening in the 55-74 age group in Ireland could reduce colorectal cancers deaths in the population from as early as the second year of the programme (10). However, as noted earlier, screening is being introduced in those aged 60-69, suggesting that it is likely to take some considerable time to have any impact on the trends in rectal cancer mortality reported here.

2.6 Conclusion

Age standardised incidence has remained static in Ireland over the period 1994-2010, although male incidence rates are significantly higher than female rates. 1-year and 5-year survival continues to increase in both sexes and is reflected in decreasing overall colorectal cancer mortality. The proportion of cases with late stage disease has increased over time, as have mortality rates for rectal cancer. In order to reduce the incidence and mortality of colorectal cancer, particularly in males, there is an urgent need for the efficient and timely roll-out of BowelScreen. Reducing incidence and mortality through screening will likely have a beneficial effect on survival, by way of earlier detection and therefore more efficacious treatment. However the narrow age-range at which BowelScreen will operate in the first instance means that the potential benefits of screening, in terms of more

advantageous stage distribution and reductions in colorectal cancer incidence and mortality in the population, are unlikely to be achieved in the short-term.

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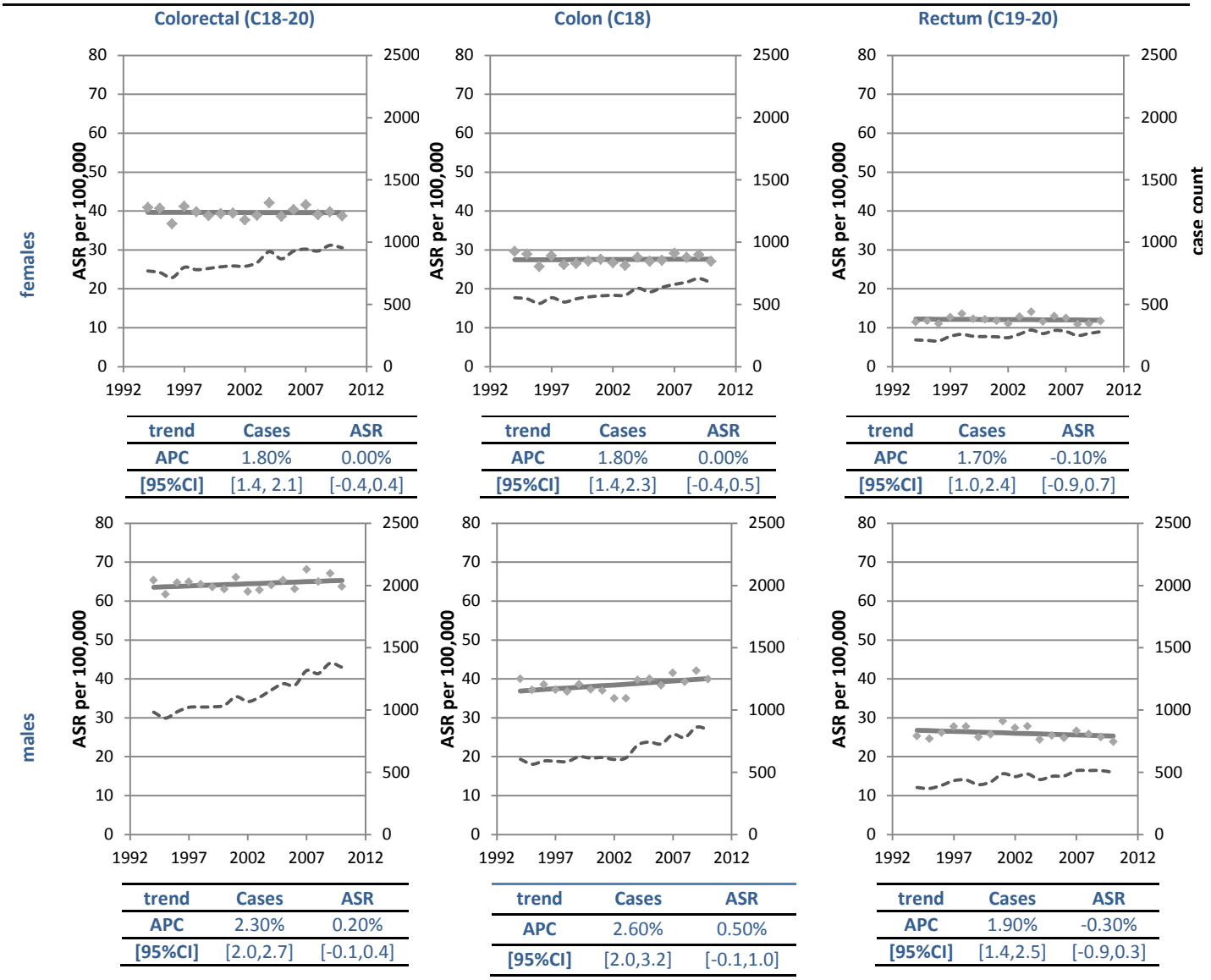
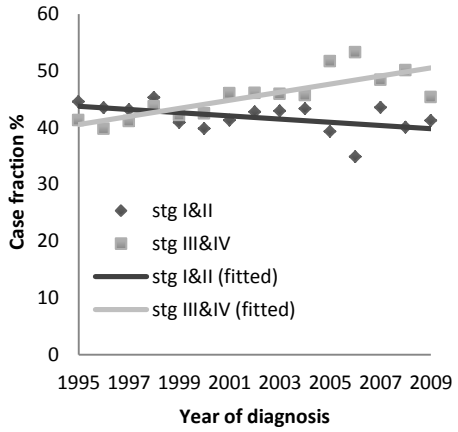


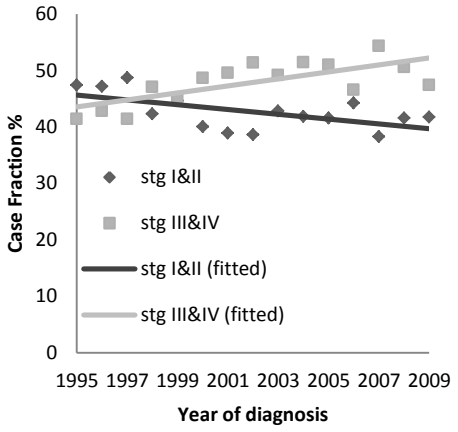
Figure 2.1: Age standardised incidence rate and incident cases of colorectal cancer by site of primary tumour and sex, 1994-2010

(A) COLON- FEMALES



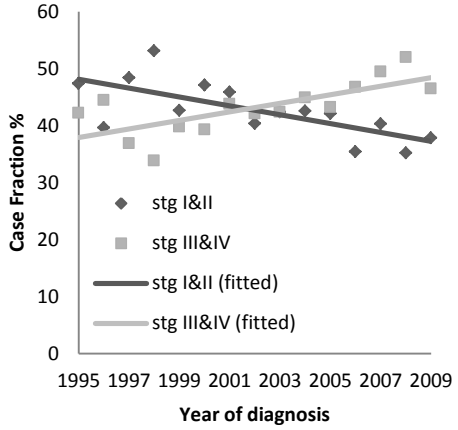
Stage of disease	From	to	APC	95%CI	Trend[a]
Stage I & II	1995	2009	-0.7%	[-1.4, 0.10%]	p=0.07↔
Stage III & IV	1995	2009	1.6%	[0.9, 2.3%]	p<0.05↑

(B) COLON MALES



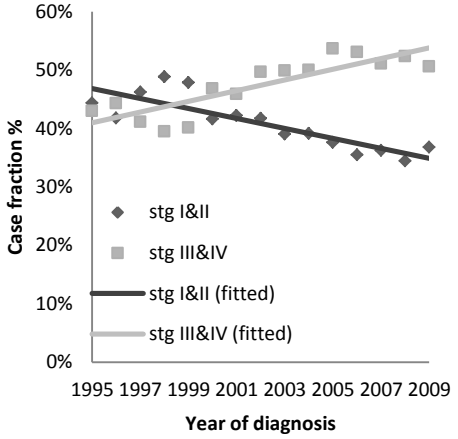
Stage of disease	From	to	APC	95%CI	Trend[a]
Stage I & II	1995	2009	-1.0%	[-1.8, -0.1%]	p<0.05↓
Stage III & IV	1995	2009	1.3%	[0.6, 2.1%]	p<0.05↑

(C) RECTUM- FEMALES



Stage of disease	From	to	APC	95%CI	Trend[a]
Stage I & II	1995	2009	-1.8%	[-2.9, -0.7%]	p<.05↓
Stage III & IV	1995	2009	1.8%	[0.7, 2.8%]	p<.05↑

(D) RECTUM - MALES



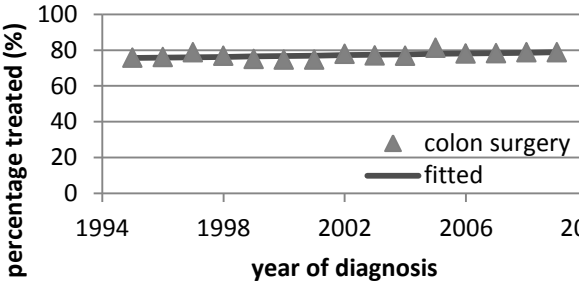
Stage of disease	From	to	APC	95%CI	Trend[a]
Stage I & II	1995	2009	-2.1%	[-2.8, -1.4%]	p=0.0001↓
Stage III &IV	1995	2009	2.0%	[1.2, 2.7%]	p=0.0001↑

[a] The p-value results are derived from a test of trend. The null hypothesis is that the APC=0%: Alternative hypothesis is APC≠0%. The APC is the slope of a log-linear regression curve from 1994-2009.

Figure 2.2: Case fraction for stage of disease at presentation, by gender and site of tumour for diagnostic period 1994-2009**. (A)** COLON- FEMALES; **(B)** COLON MALES; **(C)** RECTUM- FEMALES; **(D)** RECTUM - MALES.

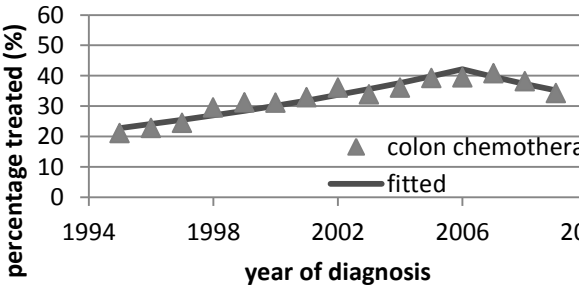
Colon (C18)

SURGERY



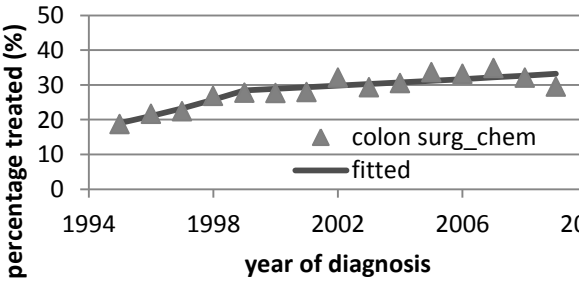
from	to	APC	95%CI	p-value
1995	2009	0.3	[0.0,0.6]	<0.05

ALL CHEMOTHERAPY



from	to	APC	95%CI	p-value
1995	2006	5.7	[4.3,7.1]	<0.001
2006	2009	-5.8	[-14.6,3.9]	0.20

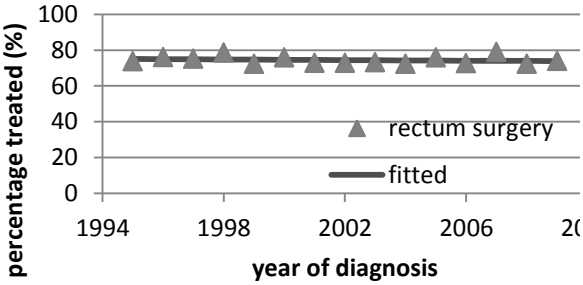
SURGERY + CHEMOTHERAPY



from	to	APC	95%CI	p-value
1995	1999	10.6	[3.6,18.1]	<0.001
1999	2009	1.5	[-0.1,3.2]	0.06

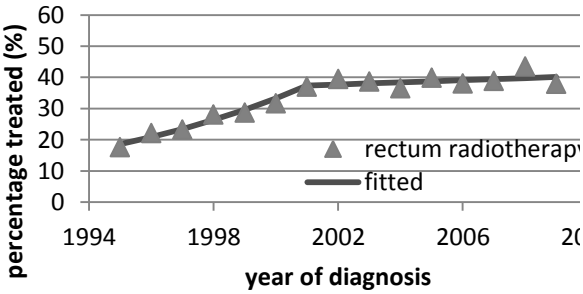
Rectum (C19-20)

SURGERY



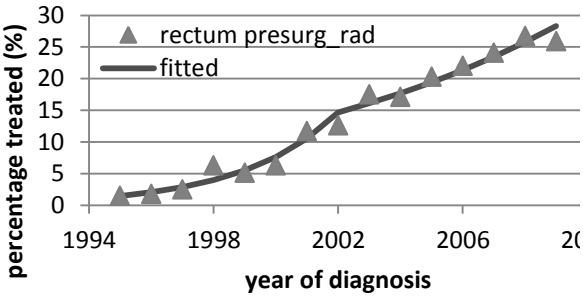
from	to	APC	95%CI	p-value
1995	2009	-0.1	[-0.5,0.3]	0.54

ALL RADIOTHERAPY



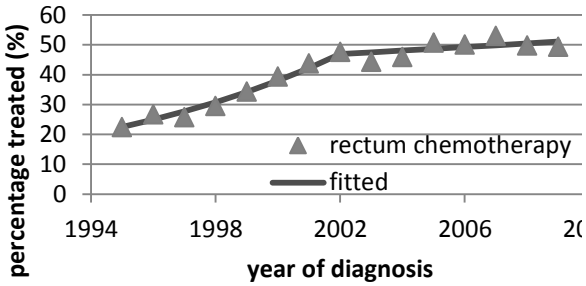
from	to	APC	95%CI	p-value
1995	20001	12.3	[9.1,15.7]	<0.001
2001	2009	0.9	[-1.0,2.8]	0.32

PRE SURGICAL RADIOTHERAPY



from	to	APC	95%CI	p-value
1995	2002	38.7	[28.7,49.5]	<0.001
2002	2009	9.9	[1.9,18.4]	0.02

ALL CHEMOTHERAPY



Key: APC=annual percentage change
Trends calculated with Joinpoint

from	to	APC	95%CI	p-value
1995	2002	11.1	[8.7,13.5]	<0.001
2007	2009	1.2	[-0.9,3.4]	0.23

Figure 2.3: Percentage of patients treated with various modalities, 1995-2009

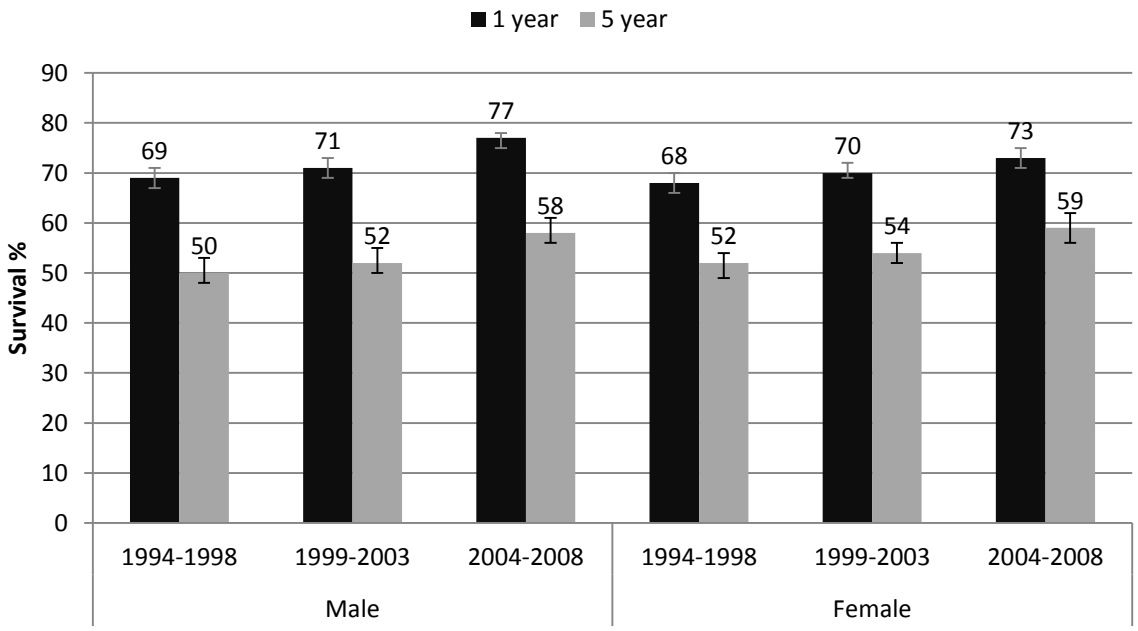


Figure 2.4: One and five year relative survival for colon cancer for diagnostic periods by sex with 95% confidence intervals

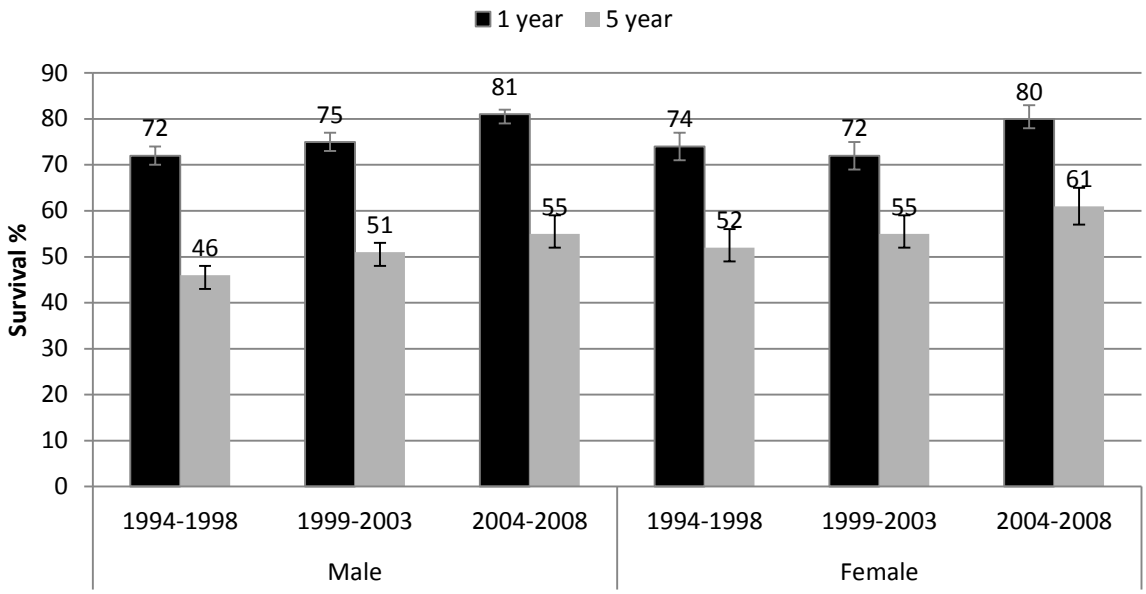


Figure 2.5: One and five year relative survival for rectal cancer by diagnostic period by sex, with 95% confidence intervals

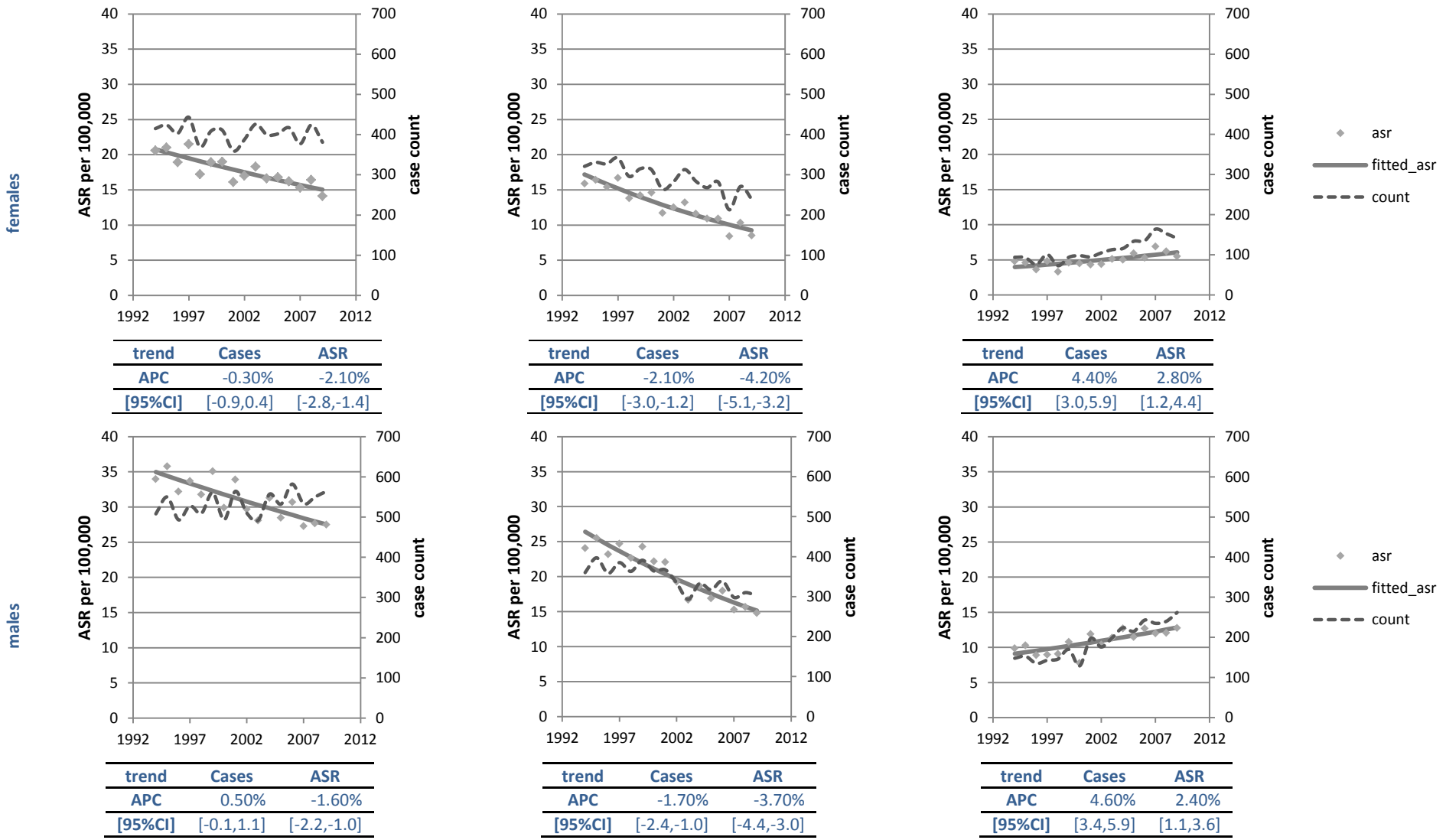


Figure 2.6: Age standardised mortality rate and number of deaths for colorectal cancer by site of primary tumour and sex, 1994-2009

3 Comparison of uptake of colorectal cancer screening based on faecal immunochemical testing (FIT) in males and females: A systematic review and meta-analysis

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3.1 Abstract

Background: Colorectal cancer is the third most common cancer in males and the second in females worldwide. Incidence and mortality are higher in men than women. CRC screening is effective in reducing mortality. Internationally, FIT is increasingly being recommended as the primary screening test. This systematic review and meta-analysis aimed to determine if uptake of FIT screening differs between men than women.

Methods: We searched PubMed and Embase for peer-reviewed papers published in English during 2000-2013 for randomised controlled trials (RCTs) or observational studies of screening using FIT which quantified numbers invited and participating by gender. Meta-analysis was performed using a random effects model.

Results: 685 citations were identified, 19 meeting the inclusion criteria. Random effects meta-analysis found male uptake was significantly lower than female uptake (odds ratio=0.84; 95% CI: 0.75-0.95; P <0.01). This generally persisted throughout subgroup analysis of study design (RCTs vs. observational studies and study quality), screening organisation (methods of invitation, number of samples, age-range of screening, recommendations and reminders) and setting.

Conclusions: Meta-analysis of FIT screening studies indicates significantly lower uptake among men.

Impact: Further investigation is required into factors influencing acceptability and participation of FIT screening in both sexes.

3.2 Introduction

Colorectal cancer is the third most common cancer diagnosed in males and the second most common in females(1).Worldwide more cases and deaths occur in males than females; with the age standardised incidence rate 44% higher (20.6 vs. 14.3 per 100,000) and age-standardised mortality 45% higher in males (10.0 vs. 6.9 per 100,000) (1). Most colorectal cancers are considered to arise from precancerous polyps; if left in situ polyps can progress to cancer over a 10-15 year period (2). However colorectal cancer can be prevented, or treated effectively if detected early, through screening (3). Evidence indicates efficacy of screening in reducing cancer mortality and, in some instances, incidence (4–8).

A number of countries have implemented population-based colorectal cancer screening programmes (9–11). Screening can be delivered through procedures conducted in a clinic or doctor's office, such as colonoscopy or flexible sigmoidoscopy (FS), or through non-invasive methods which are suitable to be undertaken in an individual's home, such as FOBT or FIT. Currently most programmes which use faecal-based tests employ FOBT (11,12). However, FIT is a more specific and sensitive test (8) and recent guidelines recommend it as the initial screening modality (3,13). In order for a screening programme to be effective in reducing mortality it needs to be well organised and requires high uptake (3). It is well established that uptake is higher for non-invasive, than more invasive, colorectal cancer screening tests(14). In addition, recent evidence suggests uptake is higher with FITs than FOBTs (15). Furthermore, some studies suggest gender differentials in uptake; uptake has been found to reverse by test modality and is higher among men for more invasive endoscopic based

procedures for both opportunistic and organised screening programmes and higher among women for non-invasive tests such as FOBTs (16–18). What remains to be established is whether there is gender difference in uptake of screening based on FIT.

The aim of this study was to conduct a systematic review and meta-analysis to determine if uptake of FIT-based screening differs by gender. A secondary aim of the study was to assess factors which may influence any gender-based differences.

3.3 Materials and Methods

Search strategy and selection criteria

Citations published in peer-reviewed English journals during January 2000 - December 2013 which reported uptake of FIT-based screening in males and females, were identified from Pubmed and Embase using a structured search strategy. MeSH terms included “neoplasms”, “malignancy”, “early detection of cancer”, “compliance”, “adherence”, “colon and “rectum”. Text word search terms included variations of ‘colorectal’, ‘bowel’, ‘colon’, ‘rectal’, ‘gastric’, ‘cancer’, ‘neoplasm’, ‘malignant’, ‘participation’, ‘compliance’, ‘uptake’, ‘attendance’, ‘FIT’, ‘faecal’, ‘fecal’, ‘immunochemical’, ‘test’, ‘kits’, ‘FOBT’, ‘iFOBT’, ‘occult’, ‘blood’ and ‘test’. One author (NC) carried out the initial screening from the search strategy to remove ineligible citations such as duplicates, conference proceedings, letters, commentary and editorials. Two authors (NC & AO) then independently determined eligibility based on the inclusion and exclusion criteria by reading the full text of the remaining papers. In order to be included in the review FIT was required to be used as a primary screening (i.e. initial) test; studies in which FIT was used for triage of people with

a positive primary screening test (e.g. FIT following gFOBT) were excluded. Studies which offered individual participants a choice of different screening tests, such as FIT or colonoscopy (i.e. in which the participant decided which test to undergo) were excluded. Studies or trials with a single group/test or multiple arms/tests and in which the screening test was assigned by the investigator were eligible for inclusion. In those with multiple arms, FIT had to be the primary test in at least one arm and only the arm(s) using FIT were included in the analysis. Studies were included if they reported: randomised controlled trials (RCTs – experimental studies in which individuals are randomly allocated to receive or not receive an intervention and then followed to determine the effect of the intervention) in which one arm involved screening by FIT; observational studies (study designs that are not randomised control trials) in which FIT was the primary screening test; or screening programmes in which FIT was the primary screening test. Studies were included if they reported numbers of people invited and screened by FIT by gender. Differences of opinion on study eligibility were resolved through discussion among the authors. A standardised form was developed to abstract data from eligible studies, including invitation and uptake figures by gender, study design, screening age range, invitation and recruitment methods, use of recommendations and reminders and number of samples required.

Quality assessment

Eligible studies were assessed for methodological quality using two instruments: the Cochrane risk of bias tool (19) for RCTs and the Newcastle-Ottawa Scale for observational studies (20). The Cochrane risk of bias tool assesses bias on six domains covering selection, performance, detection, attrition, reporting and any

other bias. For our review we assessed only selection bias (random sequence generation), reporting and other bias (comparability of confounding factors and appropriate use of statistical tests). Assessments of performance and detection bias were not carried out as many screening trials are unblinded; it is therefore likely that participants are aware of the arm to which they are assigned (21). Attrition bias or incomplete outcome data (including non-response, non-compliance or withdrawal) was not assessed because non-compliance was the outcome of interest. Cohort (study of groups of individuals, some of whom are exposed to an intervention and followed over time to determine the effect of the intervention on the outcome of interest) and cross-sectional studies (observation of a defined population at a single point in time or during a specific time interval where outcome and exposure are determined simultaneously) were assessed using the Newcastle-Ottawa Scale by awarding stars as an overall rating of three methodological factors: selection (sample representativeness (1 star) and sample size (1 star)), comparability (authors controlled for or reported confounding factors for uptake by sex and age (1 star), and for other factors such as education, marital, income or employment status (1 star)) and outcome (clear description of statistical analysis (1 star) and measurement of association or difference with confidence intervals and p values and use of appropriate statistical test (1 star)). After risk of bias assessment RCTs were also assessed for quality using the same criteria as observational studies. Studies were assessed overall based on the number of stars they had been awarded of a possible six, with 5-6 stars being considered high quality, 3-4 stars moderate quality and 2 or less stars low quality.

Statistical methods

Within each study participants were invited to complete one test. Studies which compared screening tests (multiple arms in RCTs) did not offer more than one choice of screening to each participant. Uptake was defined as the number of persons targeted (i.e. persons invited to participate in screening) who returned a completed FIT kit.

Studies were combined in a meta-analysis, conducted in Review Manager 5 (The Cochrane Collaboration, Oxford). Due to the high level of heterogeneity a random effects model was used. Subgroup analysis was also carried out to determine if the effect estimates varied by study characteristics. Subgroups were defined based on: study quality (high, moderate or low), study design (RCT or observational), age range of those invited to screening (40-75, 50 or older with no upper age limit), number of FIT samples required for test completion (1 or 2 or more samples), letter of invitation (with advance notification or without advance notification), test delivery method (test mailed to recipient or test collected by recipient) use of recommendations or endorsement of test (yes or no) and use of reminders (reminder provided or no reminder provided). Studies which did not report on these methods or which used different methods were excluded from relevant analysis. Only one study reported multiple screening rounds. This study (22) was very large (comprising 92% of the invited population and 87% of the screened population when all studies were combined) and reported six screening rounds (22). In the primary analysis this study was included with data from 2004 (round 1). Six sensitivity analyses were conducted in order to determine their impact on the effect estimate: (i) excluding this study entirely; (ii) using round 2 data (2005),

(iii) using round 3 data (2006), (iv) using round 4 data (2007), (v) using round 5 data (2008) and (vi) using round 6 data (2009).

3.4 Results

Study selection and characteristics

In total 685 potentially eligible citations were identified. Following review 19 studies were eligible for inclusion in the review and meta-analysis (22–40). A flow chart of the search strategy results is provided in Figure 3.1. Study characteristics are summarized in Table 1.1. Six were RCTs, 12 were cross sectional studies and one was a cohort study. Nine studies originated from Europe, 3 from Asia, 3 from North America, 3 from Australia and 1 from South America. Fifteen studies were population-based (i.e. studies in which screening is systematically offered by invitation to a defined population).

Across the 19 studies, a total of 2,650,358 (round 1 Park and colleagues(22)) individuals were invited to participate in FIT screening and 407451 were screened (uptake=15.4%). Excluding the largest study(22), 384,979 were invited and 169,586 screened (uptake=44.1%).

Meta-analysis

Uptake in males and females combined ranged from 11% (round 1 (22)) to 90% (26; Table 2). Meta-analysis of all included studies indicate significantly lower male uptake (Odd ratio (OR) =0.84; 95% CI: 0.75-0.95; P<0.01) (Figure 3.2). Of the 19 studies only 3 reported lower female uptake, while the remaining studies

reported lower male uptake ranging from 60% (Klushman et al: OR 0.40: 95% CI 0.21-0.80; P<0.05) to 1% (Quintero et al: OR 0.99: 95% CI 0.94-1.05; P=0.82).

Park and colleagues (22) account for 85% (round 1; round 2: 92%) of the entire screening population in the meta-analysis. In round 1 of this study, uptake was significantly higher in males than females (Odds ratio (OR) =1.16; 95% CI: 1.15-1.17; P<0.01) (Table 1.2), while in the subsequent five rounds uptake was significantly lower in males than females (Table 1.2).

When the meta-analysis was repeated replacing the round 1 results of Park and colleagues (22) with those from each of the subsequent five rounds, this had little impact on the overall risk estimate which ranged between 0.83 and 0.84 (Round 2: overall meta-analysis OR=0.84; 95% CI: 0.77-0.90; P<0.01; round 3: overall meta-analysis OR=0.83; 95% CI: 0.77-0.90; P<0.01; round 5: overall meta-analysis OR=0.83; 95% CI: 0.77-0.90; P<0.01 and round 6: overall meta-analysis OR=0.83; 95% CI: 0.77- 0.90; P <0.01). When Park and colleagues (22) was excluded entirely from the meta-analysis male uptake remained significantly lower (OR=0.83: 95% CI: 0.74-0.92; P<0.01).

Quality assessment

Of the 19 studies, 7 were deemed to be of low-quality, and 12 were considered moderate quality, while none were deemed to be of high quality. Results are summarised in Table 1.3. Moderate quality studies had significantly lower uptake in males (OR=0.81; 95% CI: 0.76-0.85; *P* <0.01) while low quality studies had non-significantly lower uptake in males (OR=0.89; 95% CI: 0.63-1.26; *P*=0.51)

however there was no significant difference in these subgroups (*P*=0.58) (Table 1.4). In addition we repeated the meta-analysis restricted to moderate quality studies only; the lower uptake in males persisted and the effect size was very similar to that seen when all studies were included (moderate quality studies only: OR= 0.83; 95% CI: 0.71-0.96; *P*=0.01).

Study design

Uptake was significantly lower in males than females in both RCTs (OR=0.83; 95% CI: 0.71-0.97; *P*=0.02) and observational studies (OR=0.83; 95% CI: 0.76-0.91; *P* <0.01) (Table 1.4). There was non-significantly lower male uptake in studies which were not part of an organised screening programme (OR=0.74; 95% CI: 0.51-1.07; *P*=0.11) as was the case for studies which were not population-based (OR=0.88; 95% CI: 0.73-1.07; *P*=0.20).

Setting

Uptake was significantly lower among males in studies based in Europe and Australia, non-significantly lower in studies based on North America and South America, and not different in studies based in Asia (Table 1.4) but, overall, subgroup differences for setting were non-significant (*P*=0.16).

Letter of invitation

The recruitment methods used in the 16 studies which described this were heterogeneous. Invitations were made from a central screening location (n=10), GP clinics (n=4), or through an index subject invited for cervical cancer screening (n=1; Table 1.1). Nine studies used a letter of invitation mailed to subjects while

three studies used an advance notification letter of invitation, mailing letters to inform subjects they would be invited and subsequently mailing a letter of invitation to participate. One study used an advanced notification letter inviting subjects to complete a bowel cancer survey, subsequently mailing a test to responders. Subgroup differences for invitation methods were non-significant (*P*=0.41). Male uptake was significantly lower in studies which did not use an advance notification letter of invitation (OR=0.77; 95% CI: 0.73-0.82; *P* <0.01) while there was non-significantly lower male uptake in studies using a letter with advance notification (OR=0.89; 95% CI: 0.64-1.23; *P*=0.47) (Table 1.4).

Test delivery method

Several studies (n=7) required the participant to collect the test from a GP, nurse or pharmacist, while 9 studies mailed the test. Subgroup differences for test delivery methods were non-significant (*P*=0.65). Male uptake was significantly lower in studies which mailed the test to participants' homes (OR=0.79; 95% CI: 0.75-0.83; *P* <0.01) and non-significantly lower in studies which required participants to collect the test (OR=0.83; 95% CI: 0.66-1.05; *P*=0.13) (Table 4).

Screening recommendations

Eight studies used recommendations or endorsement of screening, either by a GP, nurse or local Mayor. Subgroup differences were non-significant for use or non-use of recommendations (*P*=0.54). Those studies that provided a screening recommendation had non-significantly lower uptake in males (OR=0.85; 95% CI: 0.68-1.05; *P*=0.13) while there was significantly lower male uptake in studies that did not use recommendations (OR=0.79; 95% CI: 0.76-0.82; *P* <0.01) (Table 1.4).

Screening age range

Subgroup differences were non-significant for screening studies targeting different age ranges (*P*=0.28). Uptake was significantly lower in males when screening was targeted at those aged 40-75 (OR=0.79; 95% CI: 0.74-0.84; *P* <0.01) while uptake targeted at those aged 50 and over with no upper age limit was similar in males and females (OR=0.92; 95% CI: 0.70-1.19; *P*=0.51) (Table 1.4).

Fenocchi and colleagues (26) and Ferrari and colleagues (36) reported uptake by age and gender. In the former, uptake was non-significantly lower in males in people aged 50-69 (OR=0.93; 95% CI: 0.81-1.07; *P*=0.32) and those aged 70 or older (OR=0.71; 95% CI: 0.41-1.29; *P*=0.22). In the latter, uptake in males was significantly lower in those aged 50-59 (OR=0.76; 95% CI: 0.72-0.81; *P* <0.01) and in those aged 60-69 (OR=0.94; 95% CI: 0.88-0.99; *P*=0.02), but did not differ in those aged 70-71 (OR=1.05; 95% CI: 0.87-1.27; *P*=0.56).

Number of FIT samples required

Fourteen studies reported the number of samples requested; 10 studies requested one sample and four requested two or three samples over varying time intervals. The subgroup differences for the number of samples required were non-significant (*P*=0.42). The odds ratio for male uptake was significantly lower in both subgroups (One sample: OR=0.84; 95% CI: 0.71-0.98: *P*=0.03; two/ three samples: OR=0.78; 95% CI: 0.74-0.82; *P* <0.01) (Table 1.4).

Screening reminders

Ten studies reported the use of reminders (varying from 2 weeks to 6 months; Table 1.1) and two studies reported using no reminders. Male uptake was significantly lower in both subgroups (Table 1.4) with no difference in these subgroups (*P*=0.51).

3.5 Discussion

This systematic review and meta-analysis is the first to examine whether there are gender differences in uptake of FIT-based colorectal cancer screening. It provides valuable information for screening agencies relating to the implementation and delivery of programmes. Overall, uptake in males was 16% (OR 0.84 or a relative risk of 0.95: 95% CI 0.94-0.95; P<0.001) lower than in females, and this was statistically significant. While there was notable heterogeneity between studies in terms of design and screening organisation, as well as overall uptake, lower uptake in males persisted across subgroups by study design, setting, methods of invitation and delivery, use of recommendations, screening age range, number of samples and use of reminders.

Of note was the similar uptake in males and females in studies based in Asia, which contrasted with studies from other settings. Studies from Asia had similar uptake in males and females whereas studies from Europe reported lower uptake among men. While subgroup differences were nonsignificant across countries, much of the data required for inclusion in subgroup analysis was not reported in the studies from Asia. Therefore the possibility that cultural or social factors may be responsible for differential uptake in males and females cannot be entirely

discounted. It will be interesting to observe uptake of FIT-based screening in future studies within countries in Asia in comparison to Europe and Australia.

There was also no significant difference in male and female uptake in studies of low quality. Most of these required the participant to collect the test, so the effect estimate may reflect this. Test collection from a GP clinic, pharmacist or distribution centre (nurse) requires the participant to make face-to-face contact with a health professional and may act as an encouragement or endorsement of the test in addition to providing access to information about the test and how to carry it out. Studies of low quality also had quite high overall uptake, and the effect estimate may reflect this rather than the low quality per se.

Although there was no formal difference in subgroups defined by whether or not there was a recommendation or endorsement of the test, it was noteworthy that uptake was only significantly lower in males than females in studies where no recommendation was used. Other evidence suggests that lack of a doctor recommendation is an important barrier to colorectal cancer screening (41). Our findings suggest that contact with, or endorsement of the test through a health professional (GP, nurse, pharmacist) may serve to encourage men to complete the screening test. This has been noted elsewhere, where male compliance with medical procedures is increased when encouraged by a medical professional (42).

While subgroup differences were (once again) non-significant, studies which were not population-based did not have significantly lower uptake in males. Although the studies which were not population-based differed in many ways, in three of

four the screening invitation was endorsed through a GP or GP practice while two required the participant to collect the test. Therefore it cannot be ruled out that the non-significantly lower uptake in males may be a result of test collection and GP recommendation.

Age is an important predictor of colorectal cancer risk. Here male uptake was not significantly different from female uptake in studies targeting those aged 50 and over with no upper age limit. However this may be a result of the fact that some studies involved test collection (3 of the 5 studies) and/or recommendations to complete the test by a GP (4 of the 5 studies), as opposed to older men being more likely to participate in screening. Further investigation is required to assess if there is differential uptake between younger and older males in FIT-based screening and, if so, what may be driving such differences.

Cole and colleagues (24) have reported that participation in their study was significantly improved (increase in relative risk of participation of 30%) through simplification of the sampling method (using two rather than three samples); this did not differ by gender, age or socioeconomic status. In this meta-analysis, there were no subgroup differences in effect estimates according to whether studies required a single, or more, samples. Further investigation is required to assess if there is differential uptake in males and females when different FIT sampling strategies are used.

While there is tentative evidence from this review that requiring participants to collect the test, using a GP recommendation and using an advance notification

results in similar uptake in males and females, the general lack of significant subgroup differences suggest that study design or screening organisation may not be the important drivers of poorer male uptake. However results of the sub-group analysis are not necessarily definitive and reflect findings in terms of the availability of data within the included studies. There are small numbers of studies in particular sub-groups (such as advance notification). Caution is therefore warranted in the interpretation that such interventions may reduce gender based disparities. In addition not all studies reported multivariable analysis and therefore cannot definitively report that gender is independently associated with uptake. Despite this, these elements may help inform development of a taxonomy of compliance in particular groups, such as those based on sex or other background characteristics. Further research in identifying and expanding on such taxonomy is warranted. Given the dearth of evidence regarding reasons for non-participation in FIT screening in males and females, and the fact that FOBT and FIT may be considered somewhat similar from the point of view of screening invitees, it is worth considering what is known about drivers of home-based FOBT screening (non)participation. An early review of colorectal cancer screening uptake using FOBT reported that the main factors for non-compliance with screening were: conflicts with work or family, inconvenience, being too busy, or being away, lack of interest and costs (43). In addition the same review reported that non-compliance was associated with having no current health problems, being too embarrassed to complete the test, feeling the test was too unpleasant, being anxious and not wanting to know the test results (43). These findings are in line with Chapple and colleagues(44) in the UK FOBT screening programme.

The evidence base for reasons underlying gender-based differences in colorectal cancer screening uptake is very limited, and even less is known about uptake in FIT based screening specifically. Recently Ritvo and colleagues (45) suggested that males may procrastinate about colorectal cancer screening, but that, underlying this, is a deeper fatalism about cancer disease and a disbelief in the preventative-protective elements of screening. It has also been reported that males use primary care services less frequently than women (46) perhaps making them less inclined to be screened when offered the opportunity. In addition White and colleagues (46) suggest that, in Europe, the general absence of male targeted health care programmes may hinder men's ability to identify as participants in health care. These observations indicate that studies are now required exploring cultural norms surrounding, psychological and other barriers to, and facilitators of, FIT screening and how these may differ between the sexes. It would be useful to explore these barriers and facilitators through theory-based research into gender differences in preventive health behaviours.

3.6 Conclusion

Uptake of FIT-based colorectal cancer screening among males is significantly lower than among females. While studies differed in design and screening organisation methods, poorer male uptake persisted throughout subgroup analysis. Further investigation is required into why men are less likely to attend FIT screening and what factors may act as barriers or facilitators to screening uptake in men and women.

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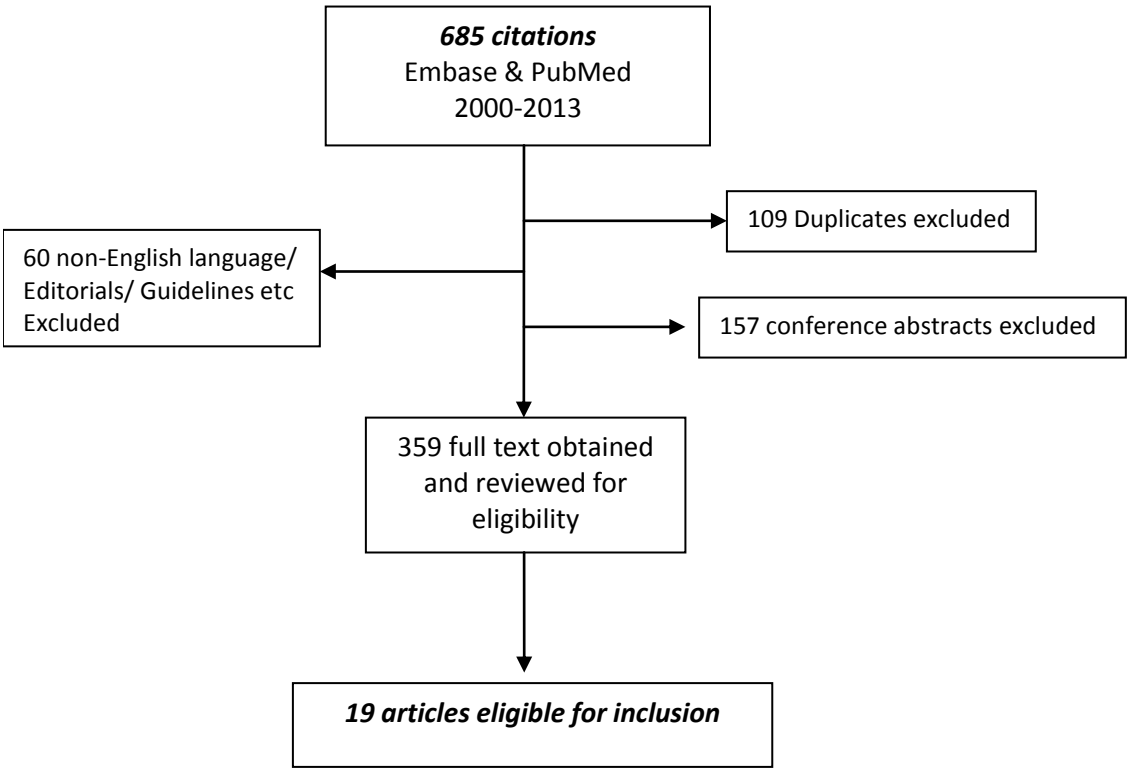

Figure 3.1: Study flow diagram: result of search strategy

Table 1.1: Characteristics of the 19 studies on FIT uptake in males and females included in the meta-analysis

Study & Year	Population based	Age range	Letter of invitation	Test delivery method	Recruitment location	Recommendation/ Endorsement	Reminder	Number of samples and interval	Test	Country
Cohort studies										
Senore and colleagues, 2012 (33)	Yes	58 & 60	No advance notification	Test collected	GP	Yes	No reminder	1	OC Sensor	Italy
Cross-sectional studies										
Fenochi and colleagues, 2006 (26)	No	50+	Not reported	Test collected	GP	Yes	2 month reminder	1	OC Hemodia	Uruguay
Gregory and colleagues, 2011 (32)	Yes	50-74	Advance notification letter to screening survey	Test mailed	Central	No	6 week reminder	Not reported	InSure	Australia
Klushman and colleagues, 2012 (38)	No	50+	Face to face recruitment	Test collected	GP	Yes	2 weeks	Not reported	INSure	USA
Crotta and colleagues, 2004 (25)	Yes	50-74	No advance notification	Test collected	Central	Yes	2 month reminder	1	OC Sensor, Japan	Italy
Chen and colleagues, 2007 (27)	Yes	50+	Not reported	Test collected	Out-reach	Yes	Not reported	1	Not reported	Taiwan
Parente and colleagues, 2009 (29)	Yes	50-69	No advance notification	Test collected	Central	No	No reminders	1	HM-Jack	Italy
Levy and colleagues, 2010 (30)	No	50-64	Advance notification	Test mailed	Central	No	Not reported	Not reported	Clearview ULTRA FOB	USA
Park and colleagues, 2011 (22)	Yes	50+	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Republic of Korea
Cai and colleagues, 2011 (31)	Yes	40-74	Not reported	Not reported	Not reported	Not reported	Not reported	2 at interval of 1 week	Not reported	China
Ferrari and colleagues, 2012 (36)	Yes	50-69	Not reported	Not reported	Not reported	Yes	Reminder - interval not reported	Not reported	Test tube	Italy
McDonald and colleagues, 2012 (37)	Yes	50-74	No advance notification	Test mailed	Central	No	Not reported	1	Eiken	Scotland
Kelley and colleagues, 2013 (40)	Yes	50-75	No advance notification	Test mailed	Not reported	Not reported	Not reported	2 at interval of 1 day	OC Sensor	Ireland
Randomised control trials										
Cole and colleagues, 2002 (23)	No	50+	No advance notification	Test mailed	Central & GP	No in 1 arm/ Yes in 2 arms	6 week reminder	3 interval not reported	Flexsure OBT	Australia
Cole and colleagues, 2003 (24)	Yes	50-69	No advance notification	Test mailed	Central	No	6 week reminder	3 (FlexSure OBT) interval not reported 2 (Insure) Interval not reported	FlexSure OBT / InSure	Australia
Gupta and colleagues, 2013 (39)	Yes	54-64	No advance notification	Test mailed	Central	No	3 week reminder	1	OC-Auto FIT CHEK	USA
Hol L and colleagues, 2012 (34)	Yes	50-74	Advance notification	Test mailed	Central	No	6 week reminder	1	OC Sensor	The Netherlands
Quintero and colleagues, 2012 (35)	Yes	50-69	Advance notification	Test collected	Central	Yes	3 and 6 month reminders	1	OC Sensor	Spain
van Rossum and colleagues, 2008 (28)	Yes	50-75	No advance notification	Test mailed	Central	No	2 week reminder	1	OC Sensor	The Netherlands

Table 1.2: Uptake figures by male and female for the 19 studies in meta-analysis with OR', 95% CI and P value

Author/ Year	*Total*			*Males*			*Females*			OR's (95%CI) *P* value
	Invited	Screened		Invited	Screened		Invited	Screened		
	n	*n*	*%*	*n*	*n*	*%*	*n*	*n*	*%*	
Park et al, 2011 Round 1 (22)	2265379	237865	10.5%	969813	105710	10.9%	1295566	123148	10.2%	1.16 (1.15, 1.17) *P* <0.05
Park et al, 2011 Round 2 (22)	3473958	538463	15.5%	1576872	238108	15.1%	1897086	299740	15.8%	0.95 (1.15, 1.17) *P* <0.05
Park et al, 2011 Round 3 (22)	4406700	691754	15.7%	2062961	307381	14.9%	2343739	384373	16.4%	0.89 (0.89, 0.90) *P* <0.05
Park et al, 2011 Round 4 (22)	4344708	782047	18.0%	2025745	350454	17.3%	2318963	433646	18.7%	0.91 (0.91, 0.91) *P* <0.05
Park et al, 2011 Round 5 (22)	4640365	983757	21.2%	2183041	447523	20.5%	2457324	538154	21.9%	0.92 (0.92, 0.92) *P* <0.05
Park et al, 2011 Round 6 (22)	4625557	1211896	26.2%	2150635	535508	24.9%	2474922	675654	27.3%	0.88 (0.88, 0.89) *P* <0.05
Cole et al, 2002 (23)	2400	857	35.7%	1094	375	34.2%	1306	482	36.9%	0.89 (0.75, 1.05) *P* =0.18
Cole et al, 2003 (24)	1212	425	35.1%	592	196	33.1%	620	229	36.9%	0.85 (0.67, 1.07) *P* =0.33
Crotta et al, 2004 (25)	2961	1631	55.1%	1403	710	50.6%	1558	921	59.1%	0.71 (0.61, 0.82) *P* <0.05
Fenocchi et al, 2006 (26)	11734	10573	90.1%	3663	3282	89.6%	8071	7291	90.3%	0.92 (0.81, 1.05) *P* =0.22
Chen et al, 2007 (27)	56968	22672	39.8%	21502	9481	44.1%	35466	13191	37.2%	1.33 (1.29, 1.38) *P* <0.05
van Rossum et al, 2008 (28)	10322	6157	59.6%	5037	2820	55.9%	5285	3337	63.1%	0.74 (0.69, 0.80) *P* <0.05
Parente et al, 2009 (29)	78083	38693	49.6%	37838	18314	48.4%	37950	20379	53.7%	0.81 (0.79, 0.83) *P* <0.05
Levy et al, 2010 (30)	297	235	79.1%	131	106	80.9%	166	129	77.7%	1.22 (0.69, 2.15) *P* =0.50
Cai et al, 2011 (31)	31963	24409	76.4%	16169	11962	74.0%	15794	12447	79.0%	0.76 (0.73, 0.81) *P* <0.05
Gregory et al, 2011 (32)	375	192	51.2%	181	86	47.5%	194	106	54.6%	0.75 (0.50, 1.13) *P* =0.17
Senore et al, 2012 (33)	37691	7281	19.3%	17223	2719	15.8%	20468	4562	22.3%	0.65 (0.62, 0.69) *P* <0.05
Hol L et al, 2012 (34)	4407	1092	24.8%	2221	472	21.3%	2186	620	28.4%	0.68 (0.59, 0.78) *P* <0.05
Quintero et al, 2012 (35)	26599	9089	34.2%	12156	4145	34.1%	14443	4944	34.2%	0.99 (0.94, 1.05) *P* = 0.82
Ferrari et al, 2012 (36)	42245	1744	41.3%	20311	7980	39.3%	21,934	9461	43.0%	0.85 (0.82, 0.89) *P* <0.05
McDonald et al, 2012 (37)	66225	38720	58.5%	32318	18058	55.8%	33907	20662	60.9%	0.81 (0.79, 0.84) *P* <0.05
Klushman et al, 2012 (38)	200	145	72.5%	50	29	58.0%	150	116	77.0%	0.40 (0.21, 0.80) *P* <0.05
Gupta et al, 2013 (39)	1593	648	40.7%	600	232	38.7%	993	416	41.9%	0.87 (0.71, 1.08) *P* = 0.20
Kelley et al, 2013 (40)	9704	5023	51.8%	4499	2177	48.4%	5205	2846	54.7%	0.78 (0.72, 0.84) *P* <0.05

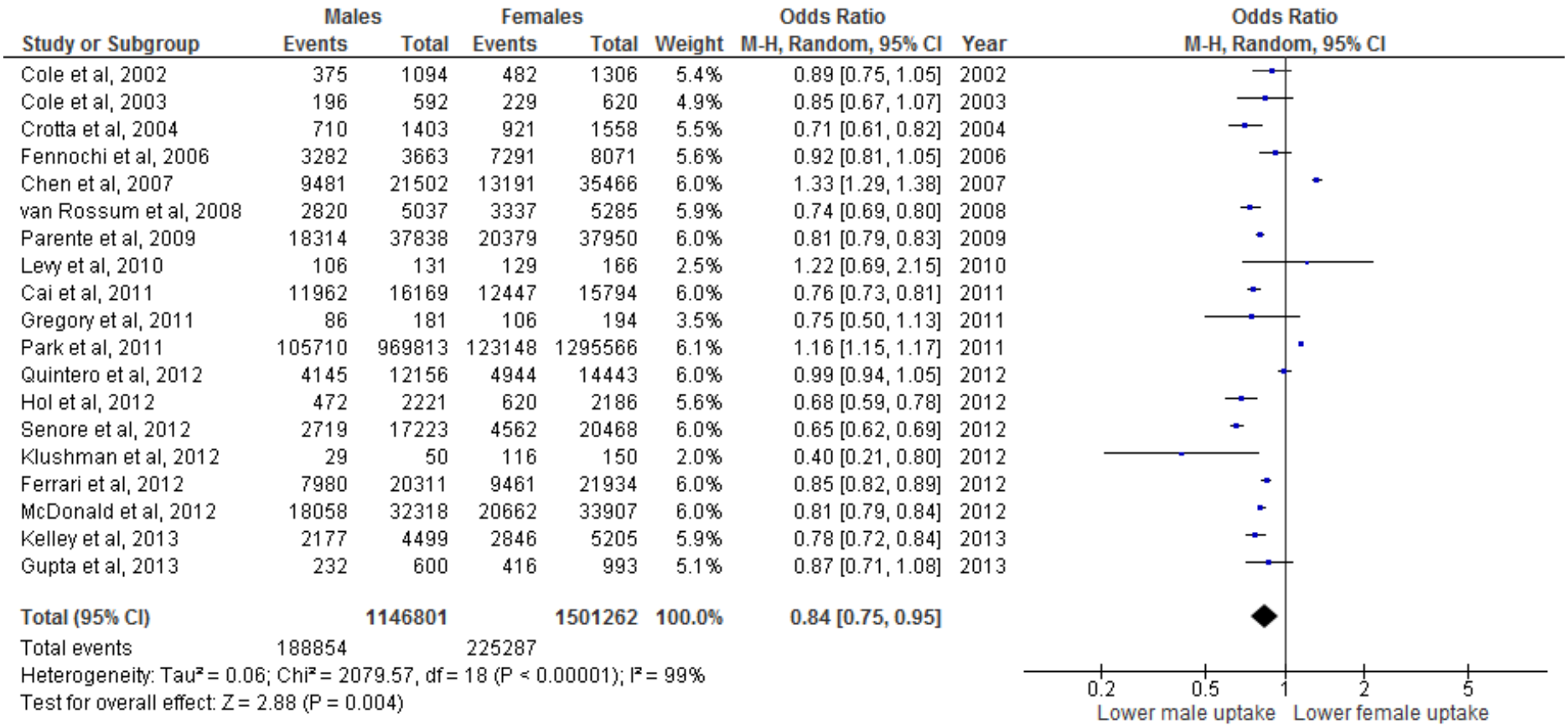

Figure 3.2: Forest plot corresponding to the main random effects meta-analysis of 19 estimates quantifying the relationship between gender and uptake of FIT-based colorectal cancer screening.

Table 1.3: Newcastle-Ottawa Scale of included studies: reviewers judgement

	Sample representativeness (Selection)	Sample size (Selection)	Counfounding controlled (comparability)	Statistical tests (Outcome)	Total stars and quality rating
Park et al, 2011 (22)	*	*		*	3/6 moderate
Cole et al, 2002 (23)	*	*		**	4/6 moderate
Cole et al, 2003 (24)	*	*		**	4/6 moderate
Crotta et al, 2004 (25)	*	*			2/6 low
Fenochi et al, 2006 (26)			*		1/6 low
Chen et al, 2007 (27)	*				1/6 low
van Rossum et al, 2008 (28)	*	*		**	4/6 moderate
Parente et al, 2009 (29)	*	*			2/6 low
Levy et al, 2010 (30)				*	1/6 low
Cai et al, 2011 (31)	*	*		**	4/6 moderate
Gregory et al, 2011 (32)	*			*	2/6 low
Senore et al, 2012 (33)	*	*		*	3/6 moderate
Hol L et al, 2012 (34)	*	*		**	4/6 moderate
Quintero et al, 2012 (35)	*	*		**	4/6 moderate
Ferrari et al, 2012 (36)	*	*	**		4/6 moderate
McDonald et al, 2012 (37)	*	*		*	3/6 moderate
Klushman et al, 2012 (38)				*	1/6 low
Gupta et al, 2013 (39)		*		**	3/6 moderate
Kelley et al, 2013 (40)	*	*		**	4/6 moderate

Table 1.4: Summary of primary and subgroup random effects meta-analysis

Sub group	*Number of studies*	*OR*	*95% CI*	I^2	*P value*
Primary meta analysis	19	0.84	0.75, 0.95	99%	**<0.01**
Study quality					
Moderate	14	0.81	0.76, 0.85	95%	**<0.01**
Low	5	0.89	0.63, 1.26	96%	0.51
Sub group differences		-	-	0%	0.58
Study design					
RCTs	6	0.83	0.71, 0.97	91%	**0.02**
Observational	13	0.83	0.76, 0.91	98%	**<0.01**
Sub group differences				0%	0.99
Study setting					
Europe	9	0.78	0.73, 0.84	95%	**<0.05**
North America	3	0.79	0.49, 1.28	68%	0.35
Asia	3	0.97	0.73, 1.28	100%	0.81
South America	1	0.92	0.81, 1.05	-	-
Australia	3	0.86	0.76, 0.98	0%	**0.03**
Sub group differences		-	-	38%	0.16
Letter of invitation					
Letter without advance notification	9	0.77	0.73, 0.82	87%	**<0.01**
Letter with advance notification[a]	3	0.89	0.64, 1.23	92%	0.47
Sub group differences		-	-	0%	0.41
Test delivery					
Test mailed	9	0.79	0.75, 0.83	45%	**<0.01**
Test collected	7	0.83	0.66, 1.05	99%	0.13
Sub group differences		-	-	0%	0.64
Recommendation					
Recommendation provided	8	0.85	0.68, 1.05	99%	0.13
No recommendation provided	7	0.79	0.76, 0.82	45%	**<0.01**
Sub group differences		-	-	0%	0.54
Screening age range					
40-75	14	0.79	0.74, 0.84	92%	**<0.01**
50+ (5)	5	0.92	0.70, 1.19	99%	0.51
Sub group differences		-	-	13%	0.28
Number of samples					
1 sample (10)	10	0.84	0.71, 0.98	99%	**0.03**
2 or more samples (4)	4	0.78	0.74, 0.82	13%	**<0.01**
Sub group differences		-	-	0%	0.42
Screening reminders					
No reminder provided	2	0.85	0.75, 0.96	73%	**0.01**
Reminder provided	10	0.81	0.73, 0.89	87%	**<0.01**
Sub group differences		-	-	0%	0.51

Note: Values in bold indicate P<0.05

[a]Advance notification indicates pre-invitation letter, followed by invitation letter

4 The role of area-level deprivation and gender in participation in population-based faecal immunochemical test (FIT) colorectal cancer screening

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4.1 Abstract

This study aimed to investigate the effects of sex and deprivation on participation in a population-based FIT-based colorectal cancer screening programme. The study population included 9785 individuals invited to participate in two rounds of a population-based biennial FIT-based screening programme, in a relatively deprived area of Dublin, Ireland. Explanatory variables included in the analysis were sex, deprivation category of area of residence and age (at end of screening). The primary outcome variable modelled was participation status in both rounds combined (with "participation" defined as having taken part in either or both rounds of screening). Poisson regression with a log link and robust error variance was used to estimate relative risks (RR) for participation. As a sensitivity analysis, data were stratified by screening round. Over both rounds of screening uptake among males was 56% and 62% among females. In both the univariable and multivariable models deprivation was strongly associated with participation. Increasing affluence was associated with higher participation; participation was 26% higher in people resident in the most affluent compared to the most deprived areas (multivariable RR=1.26: 95% CI 1.21-1.30). Participation was significantly lower in males (multivariable RR=0.96: 95%CI 0.95-0.97) and generally increased with increasing age (trend per age group, multivariable RR=1.02: 95%CI, 1.01-1.02). No significant interactions between the explanatory variables were found. The effects of deprivation and sex were similar by screening round. Deprivation and male gender are independently associated with lower uptake of population-based FIT colorectal cancer screening, even in a relatively deprived setting. Development of evidence-based interventions to increase uptake in these disadvantaged groups is urgently required.

4.2 Introduction

Colorectal cancer is the second most common cancer diagnosed in women and the third in men worldwide (1). Worldwide men have higher incidence (world age standardised rate (ASR) 20.6 vs. 14.3) and mortality (ASR 10.0 vs. 6.9) from the disease (1). Higher mortality has also been observed among lower socio-economic groups in the US and Europe (2).

Screening is efficacious and effective in reducing colorectal cancer incidence and mortality in the population (3–8). A range of screening tests are available, which detect either pre-malignant adenomatous polyps or colorectal cancers, including endoscopic-based procedures (colonoscopy and flexible sigmoidoscopy) and faecal-based tests (gFOBT and FIT). Current guidelines recommend population-based screening of asymptomatic people aged 50 years and over on an annual or biennial basis using non-invasive methods (gFOBT or FIT) or every 5 to 10 years using other - invasive - approaches (flexible sigmoidoscopy or colonoscopy) (9,10). Screening programmes require high uptake among their target population in order to maximise the health benefits, (9,11,12) and uptake of non-invasive methods is generally higher than invasive methods (13). Therefore, many population-based screening programmes use gFOBT as the initial screening test. However, FIT is increasingly being recommended as it has higher sensitivity and specificity, does not require dietary and medicinal restriction (9,10) and has been associated with higher uptake than gFOBT-based screening (14,15). Nevertheless, in current FIT-based screening programmes uptake remains low overall (16). Moreover, uptake is significantly lower among men than women and a recent systematic review concluded that screening programme design or organisation (i.e. use of letters of invitation, use of screening recommendation, test delivery

methods, use and number of reminders, number of samples required and screening age range) do not appear to be the important drivers of lower male uptake (16). Given the differences observed in uptake in males and females in Europe, Australia and Asia (significantly lower male uptake in Europe and Australia but similar uptake in males and females in Asia) it is possible that other gender-specific socio-cultural factors may be important in influencing screening acceptability.

In the UK socio-economic deprivation has been shown to affect participation in gFOBT-based colorectal cancer screening (17). Results from a Scottish study showed that use of FIT as the primary screening test improved uptake compared to gFOBT, particularly among the most deprived and men, although many participants had been exposed to gFOBT for a number of years prior to the offer of FIT (15). As far as we are aware these are the only studies that have examined how FIT might reduce disparities over gFOBT screening. In addition relatively little is known about whether there are deprivation gradients in uptake of FIT-based screening and, in particular, whether gender and deprivation might operate independently in influencing participation.

Understanding socio-demographic predictors of screening participation is important because unequal access across groups runs the risk of creating or widening health inequalities (18). During 2008-2012 a population-based FIT-based screening programme ran in Tallaght, a district of Dublin (19). In this setting, we investigated the effect of sex and deprivation on FIT-based screening uptake.

4.3 Methods

Study setting

Tallaght is one of the largest towns in the County of Dublin and has a population of just under 70,000 people (20). The area is identified as one of the most disadvantaged in Dublin (and, therefore, in Ireland). Ireland has a mixed public-private healthcare system. Care within the public system is available to all citizens. Unless an individual has a "medical card" (which is available to those on reduced means) they must pay to see a general practitioner (GP) and make modest co-payments for hospital in-patient and out-patient services. Just under half of the population have private health insurance; this generally covers hospital care. The screening programme, and any associated follow-up investigations or treatment, was provided free of charge to all invitees.

The Tallaght Hospital/ Trinity College Dublin Colorectal Cancer Screening Programme (TTC-CRC-SP) offered two rounds of biennial screening. 9785 individuals between the ages of 50-74, and resident in Tallaght, were identified through seven primary care practices and invited to participate in screening (21). Individuals were sent a FIT kit with an initial invitation letter. The invitation pack also contained information on colorectal cancer and an Irish Cancer Society help-line telephone number was also provided. The programme was not promoted beyond the invitation letter; therefore all invitees received identical information. Participation in the programme was free to all participants, as was treatment if cancer was detected. Reminders were sent to non-responders. The first screening round was completed during 2008-2010 and the second during 2011-2012. At the commencement of round two individuals were excluded if they had left the

catchment area after round one, had been diagnosed with colorectal cancer in round one or were known to have died. Non-responders to round one invitation were included sent an invitation to participate in round two.

For analysis we included the available explanatory variables which were sex, age and deprivation category of the area in which the individual lived (21). The NCRI geo-coded the addresses of residence of those invited to participate in the TTC-CRC-SP, in order to enable individuals to be assigned to an area-level deprivation category based on the Pobal Haase Pratschke (HP) Deprivation index (21). This index (based on the 2006 and 2011 census waves), which is assigned to small areas, is based on the following characteristics of the population resident in the area: population density, age dependency ratio, lone parent ratio, primary education only, third level education, unemployment rate and proportion living in local authority rented housing (21). The index is divided into 8 categories ranging from extremely disadvantaged to extremely affluent. Age (at completion of the two screening rounds) was divided into five categories for analysis: (i) <60, (ii) 60-64, (iii) 65-69, (iv) 70-74 and (v) 75+. As all invitees were included in both rounds some invitees were older than the initial screening criteria age range at the outset of round 2 (i.e. those who were aged 74 years during round 1 were aged 75 or over during invitation to round 2).

The outcome variable was uptake status (participant or non-participant) and the primary analysis was based on the two screening rounds combined. In the primary analysis, participants were defined as those who took part in either or both screening rounds; non-participants took part in neither round. Uptake was calculated as the percentage of individuals who completed a screening test out of the total number invited to participate. We excluded individuals from the analysis

if: they had died prior to screening (n=201); they self-referred to screening (n=16); they had completed someone else's test (n=16) they were medically unsuitable for screening (n=94); the recorded address was incorrect (n=245); or a deprivation category could not be assigned to their address (n=62) (Figure 4.1). A sensitivity analysis was undertaken to investigate uptake separately by screening round.

All analysis was conducted using Stata 11. We compared characteristics of participants and non-participants using chi-square tests. As the outcome was common (greater than 10%), (22) we did not use logistic regression for estimation, rather we modelled participation status using Poisson regression with a log link and robust error variance (23) to estimate relative risks (RR) for participation. All three explanatory variables were fitted separately, then simultaneously. Variables were included in the final multivariable model if the *p* value from the associated Wald test was <0.05. We tested for interactions between the explanatory variables by fitting cross-product terms to a model containing all main effects.

Three sensitivity analyses were conducted. We stratified the data by screening round and analysed the following three outcomes separately: uptake in round 1 (participants in round 1 vs. non-participants in round 1); uptake in round 2 (participants in round 2 vs. non-participants in round 2); and uptake in both rounds (participants who participated in both round 1 and round 2 vs. non-participants in either round (those who participated in only one round of screening were excluded from this sensitivity analysis)) (Figure 3.1).

4.4 Results

Table 2.1 summarises the characteristics of the 9151 screening invitees included in the analysis. Of these, 46% were male. The mean age at the end of screening was 62 years (Inter Quartile Range (IQR): 57-66. Invitees were resident in only five of the eight possible deprivation categories (very disadvantaged, disadvantaged, marginally below average, marginally above average and affluent). None of the study participants were resident in areas classified as extremely disadvantaged, very affluent and extremely affluent (21); and almost half (48%) were from very disadvantaged or disadvantaged areas.

Overall, uptake in males was significantly lower than uptake in females ($p<0.001$). This was also seen for round one only ($p=0.002$). There was no difference in uptake in males and females in round two only ($p=0.146$). Among invitees, the distribution of deprivation did not differ by sex ($p=0.145$; similar to the national population (24)) but the distribution of age did ($p=0.002$); 38% of female invitees were aged <60 compared to 35% of males, with a slightly higher proportion of males in the 70-74 age group (13% vs 11%).

Uptake in both screening rounds combined was 60%; 41% of invitees took part in both rounds, 8% in round 1 only and 10% in round 2 only; 40% did not take part in either round. A higher percentage of females participated in screening (both rounds combined: females 62% vs. males 56%) (Table 2.1). This translated into a significantly lower relative risk of participation in males than females in univariable analysis (RR=0.96: 95%CI 0.95-0.98) (Table 2.2). Uptake was significantly higher in all age groups compared to those aged less than 60 (Test of linear trend across groups: RR=1.02: 95%CI 1.01-1.02; *p* (trend) <0.001) (Table

2). Deprivation was strongly associated with uptake; compared to those in very deprived areas the relative risk for those resident in affluent areas was 1.22 (95% CI 1.17-1.27; Table 1.2). In a test for trend the relative risk of uptake increased by 6% for each category of increasing affluence (RR=1.06: 95% CI 1.05-1.06; *p* (trend) <0.001).

In the multivariable model sex remained a significant predictor of uptake after adjusting for deprivation and age; males had a 4% lower relative risk of participation than females (RR=0.96: 95% CI 0.95-0.97; Wald test p <0.001)). Age was also a significant predictor of uptake (Wald test p <0.001); those in older age groups had higher relative risks of participation than those aged less than 60 (although the effect was not significant in those aged over 75). In a test for trend, uptake increased by 2% (RR 1.02: 95% CI 1.01-1.02; p (trend) <0.001) for each increasing age category. Deprivation was a strong predictor of uptake (Wald test p<0.001) and the relative risk of participation was 26% higher in those resident in affluent compared to very disadvantaged areas (RR=1.26: 95% CI 1.21-1.30) (Table 2.2). In a test for trend, the relative risk of uptake increased by 6% per unit increase in affluence (RR=1.06: 95%CI 1.05-1.07). Therefore the effect of deprivation was not attenuated by age or sex. No significant interactions were found between the socio-demographic variables (age*sex; p (interaction)=0.35; sex*deprivation; p (interaction)=0.16; deprivation *age; p (interaction)=0.17) (data not shown).

In the sensitivity analysis, the effects of deprivation and sex were most pronounced in screening round 1. For round 1, relative risk of participation was more than three-times higher in those resident in affluent compared to very deprived areas (multivariable RR=3.32: 95% CI 2.28-4.83) and males had almost

20% lower relative risk of participation than females (multivariable RR=0.81: 95% CI 0.71-0.92). For round 2, deprivation was a significant predictor of uptake, but sex was not. Participation in both rounds was significantly associated with affluence (affluent vs. very deprived multivariable RR=2.34: 95% CI 2.04-2.67), female sex (males vs. females multivariable RR=0.87: 95% CI 0.83-0.91), and older age (over 75 vs. <60): multivariable RR=1.22: 95% CI 1.07-1.39) (Supplementary table 1.1).

4.5 Discussion

Poor screening uptake and socio-economic status are a largely unmet challenge in research and threaten potential increases in inequalities in cancer mortality (18). Our study shows - for the first time as far as we are aware - that deprivation is the strongest socio-demographic predictor of uptake in population-based FIT-based screening. This effect remained after adjustment for gender and age, and persisted across screening rounds. Given that our study was based in a predominantly deprived area of a large European city it was also notable that there was a significant difference in uptake even within the least affluent sectors in our study population (i.e. uptake was significantly higher among people resident in disadvantaged compared to very disadvantaged areas). While our study primarily set out to examine gender based differences in uptake, the stark differences in uptake by deprivation warrant particular attention given the much greater effect of deprivation on screening uptake. This should also be a focus of future research and interventions as an area in which uptake gains can be achieved. A nationwide FIT-based screening programme, BowelScreen, began to roll-out in Ireland in late 2013 (www.bowelscreen.ie). Given our study was conducted in an area which does not contain the extremes of the deprivation index (i.e. extremely deprived

and extremely affluent) we would speculate that, in BowelScreen, the differences in uptake observed may be even larger than those seen in our study.

Associations between poor uptake of colorectal cancer screening (using a range of tests other than FIT) and lower socioeconomic status (measured at both the individual and area level) have been reported in the literature (17,25–28). Our results are consistent with – and extend - these. Others have found that, overall, FIT-based screening is usually associated with higher uptake than gFOBT-based screening (which has traditionally been used in population based screening programmes) (14). If we compare uptake rate by area –level deprivation category in this study, with those reported in the English gFOBT-based screening programme, rates in the current study exceed those in England in every deprivation category. While some caution is needed here, as the deprivation indices and categorisations differ in the two populations, our findings tentatively suggest that use of FIT may result in higher uptake (compared to gFOBT-based screening; (17)) even among those resident in more deprived areas.

Solmi et al found that after controlling for several socio-demographic, economic and health variables there was an independent association between limited wealth and lower probability of participation in colorectal screening (27). This study was a longitudinal cohort study based on self-reported data of ever taking part in screening. In a decomposition analysis the authors report that health literacy contributed to 8% of the inequality in screening uptake; inadequate health literacy was associated with lower screening uptake and this was independent of individual-level measures of socio-economic status (27). Health literacy is the degree to which individuals have the capacity to obtain, process and understand basic health information and services in order to make appropriate health

decisions (29). Educational attainment and social status are positively associated with health literacy (30). While we did not have data on education in our study, data is available on the levels of educational attainment for the area in which our study was carried out. More than one-third (33% - 39% across sub-areas) of the adult population of Tallaght have only primary education, more than twice the national average (16%; (21). In the UK having adequate health literacy has been associated with higher participation in gFOBT-based colorectal cancer screening (OR=1.20: 95% CI 1.00-1.44) (31). Von Wagner et al have suggested that written invitations, the route through which individuals are invited to participate in colorectal cancer screening in the UK, may be difficult to process and understand for adults with limited health literacy (32). In our study individuals were invited to participate in writing and the invitation contained a printed leaflet with information about the screening test and how to complete it. However the possibility does exist that differences in health literacy between those resident in deprived and more affluent areas could explain some of our findings. While health literacy is correlated with reading ability they are different. Further research on uptake, education, reading and health literacy is warranted in exploring the potential underlying mechanisms of poorer uptake in males and more deprived areas in this screening population.

Generally uptake reported here (60%) was broadly similar to uptake of population based studies reported in the systematic review in chapter 3 where uptake ranged from 25% to 60% in studies in the Netherlands, from 19% to 55% in studies from Italy and 35% to 51% in studies from Australia (note that many of these studies had different methodologies). Our study also shows that male sex is associated with lower relative risk of participating in FIT-based screening and that this effect

is independent of age and deprivation. The absence of interaction between deprivation and gender suggest that lower uptake in males is not moderated by deprivation levels. This extends findings from our recent systematic review which observed that men had lower FIT uptake in almost every setting, but which was unable to determine if this effect was independent of other socio-economic factors (16). The systematic review on male uptake reported an odds ratio of lower male uptake of 16% (OR 0.84), which when converted to a relative risk (excluding the largest study which is unlikely to be compatible with the situation in Ireland or indeed Europe), is 0.95 (95% CI 0.94-0.95; P<0.001) which is almost identical to the RR for male uptake reported here (RR 0.96: 95% CI 0.95-0.97; P<0.001).

Men in Ireland have significantly poorer health literacy and functional literacy than women, (33) suggesting that health literacy could also explain the observed lower uptake in men. However, other factors could be in operation. For example, Miles et al have reported that poor self-rated health significantly mediated the relationship between uptake and socio-economic status (34). In a qualitative study nested within the TTC-CRC-SP, we found that several factors appeared to influence non-use of FIT-based screening, and that these factors differed by gender; drivers of non-participation in males included fear of cancer, fatalism, lack of knowledge and being misinformed whereas negative attitudes, beliefs, emotions and social influences influenced females non-use (35). In a study on late stage colorectal and lung cancer diagnosis, females had higher fatalism scores than males, (36) and those with lower income and lower educational attainment also had higher levels of fatalism. Other studies have found associations between cancer fatalism, lower income/educational attainment, poor self-rated health (34,37) and lower screening uptake. We have also found differences in fatalistic

beliefs in our qualitative work in this population (35) suggesting differences may exist at the screening population level in cancer fatalism between men and women (or, indeed by deprivation status). This however needs to be investigated further.

However, these explanations are speculative and further research is required to better understand what underlies the observed differences in uptake. It would be particularly useful to examine if a gender difference exists in screening information comprehension and subsequent decisions to participate in FIT-based screening – both in Ireland and more widely. It is important also to understand the mechanisms by which fatalistic beliefs and lack of cancer knowledge (which are not necessarily exclusive of one another) may contribute to low screening uptake and how these may differ by sex and socio-economic status. Some evidence is beginning to emerge on success in intervention trials aimed at tackling the socioeconomic gradient in colorectal cancer screening uptake through mailed materials (38). Future investigations should examine if poorer health literacy in males (and/or the most disadvantaged groups of the population) may be amenable to interventions to improve screening uptake in this population. In the meantime, we concur with Von Wagner et al (32) that screening programmes should seek to simplify messages and make screening information more accessible to different sectors of the population.

Our study had several limitations. Firstly there was limited data available to us and the variables on which we did have information were not modifiable. In addition screening history was not available to us and as such we could not determine the extent to which prior screening may have influenced uptake. However when the TTC-CRC-SP started, no other organised colorectal screening programme was in operation in Ireland, so any previous related tests participants

may have had would have been opportunistic or diagnostic. We were also unable to determine any effect of multiple invitations in individual households on uptake.

4.6 Conclusion

In conclusion, our study shows that FIT-based screening uptake is lower in more deprived sectors of the population and in men, and that these are independent effects. It is important to investigate what underlies these findings to inform the development of interventions to reduce and, ideally, eliminate these disparities. Failure to intervene effectively will ultimately mean that these groups will experience a disproportionately greater burden of colorectal cancer.

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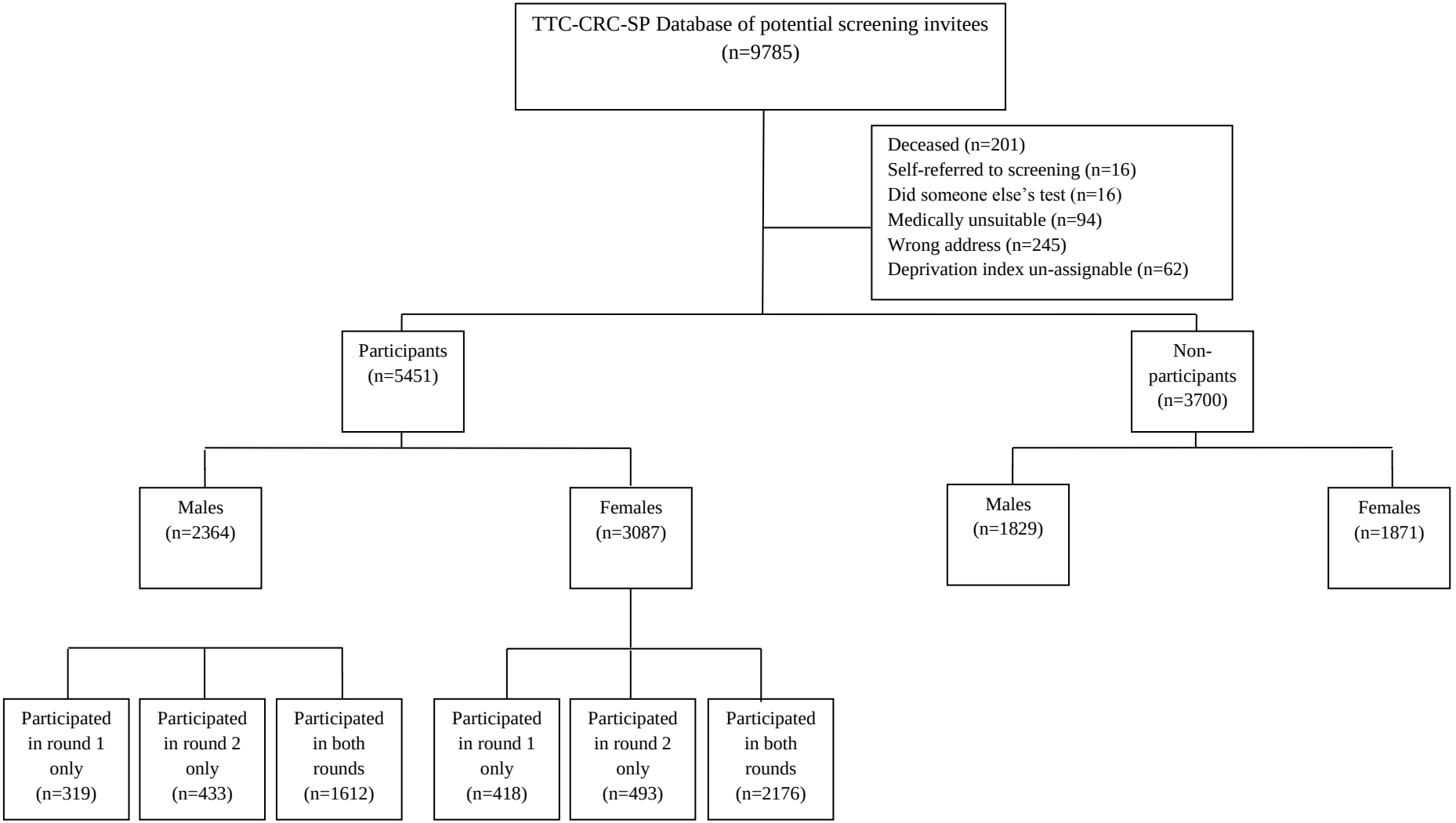

Figure 4.1: Consort diagram of TTC-CRC-SP invitees

Table 2.1: Characteristics of screening invitees of the TTC-CRC-SP

	Total		Male		Female	
Participant characteristics	N	(%)	N	(%)	N	(%)
Participation						
Participation overall	5451	(60)	2364	(56)	3087	(62)
Both rounds	3788	(41)	1612	(38)	2176	(44)
Round 1 only	737	(8)	319	(8)	418	(8)
Round 2 only	926	(10)	433	(10)	493	(10)
Non-participant	3700	(40)	1829	(44)	1871	(38)
Age[a]						
Mean age (IQR[b])	62 (57-66)		62 (58-67)		61 (57-66)	
<60	3276	(37)	1419	(35)	1857	(38)
60-64	2633	(30)	1212	(30)	1421	(29)
65-69	1899	(21)	896	(22)	1003	(21)
70-74	1048	(12)	522	(13)	526	(11)
75+	66	(1)	27	(1)	39	(1)
Deprivation[c]						
Very disadvantaged	1193	(13)	521	(12)	672	(14)
Disadvantaged	3068	(34)	1374	(33)	1694	(34)
Marginally below average	3851	(42)	1800	(43)	2051	(41)
Marginally above average	872	(10)	416	(10)	456	(9)
Affluent	167	(2)	82	(2)	85	(2)

[a] Age was not available for 229 invitees; [b]IQR: Inter quartile range; [c]Missing categories from POBAL HP deprivation index: Extremely Disadvantaged, Very Affluent and Extremely Affluent

Table 2.2: TTC-CRC-SP Absolute uptake by participant characteristics (numbers and %) and univariable and multivariable relative risks (RR) for participation in FIT-based colorectal cancer screening with 95% confidence interval and p values: primary analysis based on two screening rounds combined[a]

	Invited	Participated		Univariable model		Wald	Multivariable model[b]		Wald
	N	N	(%)	RR	95%CI	p	RR	95%CI	p
Sex									
Female	4958	3087	(62)	1.00	-		-	-	
Male	4193	2364	(56)	0.96	0.95 - 0.98	<0.001	0.96	0.95 - 0.97	<0.001
Age									
<60	3276	1874	(57)	1.00	-		-	-	
60-64	2633	1618	(61)	1.03	1.01 - 1.04		1.03	1.01 - 1.04	
65-69	1899	1260	(66)	1.06	1.04 - 1.08	<0.001	1.06	1.04 - 1.08	<0.001
70-74	1048	650	(62)	1.03	1.01 - 1.05		1.03	1.01 - 1.05	
75+	66	44	(67)	1.06	0.99 - 1.14		1.05	0.98 - 1.12	
Test of trend[c]				1.02	1.01 - 1.02		1.02	1.01 - 1.02	
Deprivation									
Very disadvantaged	1193	548	(46)	1.00	-		-	-	
Disadvantaged	3068	1643	(54)	1.05	1.03 - 1.08		1.06	1.04 - 1.08	
Marginally below average	3851	2542	(66)	1.14	1.11 - 1.16	<0.001	1.14	1.12 - 1.16	<0.001
Marginally above average	872	588	(67)	1.15	1.12 - 1.18		1.16	1.13 - 1.19	
Affluent	167	130	(78)	1.22	1.17 - 1.27		1.26	1.21 - 1.30	
Test of trend[c]				1.06	1.05 - 1.06		1.06	1.05 - 1.07	

[a] Participation defined as taking part in either or both screening rounds; [b] Mutually adjusted for sex, age and deprivation; c Linear trend across categories

5 Impact of gender on decisions to participate in Faecal Immunochemical Test-based colorectal cancer screening: A qualitative study

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5.1 Abstract

Introduction: FIT is increasingly being used in population-based colorectal cancer screening programmes. Uptake of FIT is lower in men than women however the reasons for this are not well understood. We aimed to explore gender differences in influences on decisions to participate in FIT screening.

Methods: A qualitative study using in-depth face to face interviews of four groups of screening invitees (male and female screening users; male and female screening non-users), purposively sampled from the database of a population-based FIT screening programme. Recruitment continued until saturation was reached. Interviews were audio-recorded and transcribed verbatim. Thematic analysis using the Framework approach was employed with the Theoretical Domains Framework (TDF) guiding analysis.

Results*:* 47 screening invitees (8% response rate [56% among users and 3% among non-users]) were interviewed. Six TDF domains influenced screening uptake: "environmental context and resources", "beliefs about capabilities", "beliefs about consequences", "emotions", "social influences" and "knowledge". Male non-users were often fatalistic, less knowledgeable, and misinformed about cancer and FIT screening compared to other groups. Female non-users expressed negative attitudes, beliefs and emotions towards FIT screening, cancer, social influences and the medical profession, and were over-confident about their health.

Conclusions: Negative attitudes and emotions to screening dominated non-user decision-making but differed by gender. Opportunities to improve uptake in men and women exist. Greater national discussions on the benefits of FIT screening, and development of screening materials tackling negative attitudes and beliefs while recognising male/female differences, may improve screening uptake.

5.2 Introduction

Worldwide, colorectal cancer is the second most common cancer diagnosed in women and the third most common in men although men have higher incidence and mortality from the disease. (1) Screening is effective in reducing colorectal cancer incidence and mortality. (2–7) Current guidelines recommend population based-screening of asymptomatic people aged 50-74 years or ≥50 years annually or biennially using non-invasive methods (gFOBT or FIT) or every 5-10 years using other procedures (flexible sigmoidoscopy/colonoscopy). (8, 9) Many population-based screening programmes employ FOBT as the initial screening test. However FIT is increasingly being recommended because it has higher specificity and sensitivity (8) and higher uptake. (10, 11)

In order to be effective in reducing incidence and mortality, population-based screening programmes require high uptake. Males have higher uptake of endoscopy-based screening procedures, while females have higher uptake of non-invasive tests such as FOBT and FIT. (12–14) For FIT specifically, a recent systematic review and meta-analysis estimated that the odds of screening participation was significantly lower in males compared to females (odds ratio [OR], 0.84; 95% CI, 0.75–0.95). (15) However the drivers of lower male uptake did not appear to be related to screening programme design or organisation. (15)

Lower colorectal cancer screening uptake in men has been associated with poorer knowledge of colorectal cancer and screening (16,17); lower perceived severity of colorectal cancer; fatalistic beliefs about cancer; procrastination; lower beliefs about capabilities of successfully completing testing; machismo and homosexual sensitivities. (16,18,19) Higher uptake in women has been associate with having a

family member with colorectal cancer [20] while lower uptake has been associated with fear of endoscopic based procedures and fear of a positive diagnosis. (16) However, this evidence relates to FOBT or endoscopic based tests; evidence on reasons for gender differences in uptake of FIT specifically is lacking.

We used a qualitative approach to explore differences in male and female influences on use and non-use of a population-based FIT colorectal cancer screening programme.

5.3 Methods

Design

In-depth semi-structured interviews were conducted among people invited to participate in the Tallaght Hospital/ Trinity College Dublin Colorectal Cancer Screening Programme (TTC-CRC-SP), a population-based FIT-based colorectal cancer screening programme in Tallaght, one of the most disadvantaged areas of Ireland. (20, 21) Approximately 10,000 people aged 50-74 were identified through primary care practices and invited by mail to participate in screening; the FIT kit was sent with the initial invitation. Round 1 operated during 2008-2010 (uptake was 51%) and Round 2 during 2011-2012 (uptake was 47.5%). (22) In both rounds uptake was significantly lower among men than women (e.g. round 2: 44.5% vs. 50%; OR 0.79: CI 0.73-0.89). (22) The TTC-CRC-SP ceased in December 2012 after two screening rounds and, in 2013 a national FIT based screening programme (BowelScreen) began (http://www.bowelscreen.ie).

Theoretical Framework

The Theoretical Domains Framework (TDF) (23) was used as a framework for examining potential influences on whether individuals accepted an invitation to participate in the TTC-CRC-SP. The TDF integrates 33 psychological and organisational theories to provide a comprehensive framework of possible influences on behaviour. (23) It consists of 14 domains (23): knowledge, skills, social/ professional role and identity, beliefs about capabilities, optimism, beliefs about consequences, reinforcement, intentions, goals, memory attention and decision processes, environmental context and resources, social influences, emotion, and behaviour regulation.

Recruitment and interviews

A purposive sample was drawn from the TTC-CRC-SP database (supplementary figure 1). "Users" were defined as those who had taken part in either or both screening rounds; "non-users" did not take part in any screening round. Screening invitees were stratified into four groups according to participation status (users/non-users) and gender (male/female). Each group was sorted alphabetically in Microsoft Excel by surname and forename and a random number assigned to each person (using the RAND function). We re-sorted each group from lowest to highest number and approached people in sequence, starting with the lowest numbered individual. The study was approved by the St James/Adelaide Meath Hospital incorporating the National Children's Hospital Research Ethics Committee (REC Reference 2013/12/05).

Potential interviewees were contacted by mail and invited to be interviewed. Those who returned a reply slip were telephoned by the male interviewer (NC)

who answered any questions and arranged a convenient time and place for the interview. All participants provided written informed consent. Interviews were conducted face-to-face, at the participant's home, the local hospital or another venue, according to the interviewee's preference, during May-August 2014. Everyone who accepted and was available to take part was interviewed. Recruitment continued until saturation was reached (i.e. no new themes emerging across all interviews). Interviews were audio recorded with the interviewee's permission and lasted 15-90 minutes (mean=41 minutes).

Topic guide

The topic guide (Supplementary Table 2.1) was informed by the TDF. Questions were developed for each domain to explore potential influences on screening invitees' decisions regarding FIT screening use.

Analysis

Transcripts were imported into NVivo 9. Data were analysed thematically using the Framework approach; this involved familiarisation, construction of a thematic framework (the TDF domains), indexing and sorting data, and reviewing data extracts. (24) Two researchers independently read four transcripts, coded these to the TDF domains then discussed coding to reach consensus. The remaining interviews were then coded to the TDF by one researcher (NC). A health psychologist (PG) was consulted when necessary. Domains were compared and contrasted by strata. Selected illustrative quotes are presented in Tables 3.1 (users) and 2 (non-users), with additional quotes in Supplementary Tables 2.2 (users) and 2.3 (non-users).

5.4 Results

Interviews were conducted with 47 people (response rate of 8%), 28 users of FIT-based screening (16 male, 12 female) (response rate of 56%) and 19 non-users (9 male, 10 female) (response rate of 3%). Interviewees' characteristics are summarised in Supplementary Table 2.4.

Six TDF domains were identified as influencing interviewees' decisions on participation in FIT-based screening: 'environmental context and resources', 'beliefs about capabilities', 'beliefs about consequences', 'social influences', 'emotions' and 'knowledge' (Supplementary Table 2.5).

Environmental context and resources

Screening users

A prominent influence on screening behaviours was salient events in interviewees' lives. These acted as a catalyst encouraging screening participation in male and female users. Generally these related to others diagnosed with cancer or other gastric/bowel conditions and were a context within which screening was validated as a positive health behaviour.

Resources and materials relating to the FIT kit also influenced participation. Most female users found the test equipment simple and easy to use. In a few instances females raised concerns with the kit (e.g. paper for catching stool, sampling tool, packaging for storing the sample in the refrigerator); these issues were overcome and did not act as barriers to participation. Male users were very positive about the screening resources and materials provided.

Screening non-users

Female non-users referred to salient events related to colorectal cancer, other cancers or other gastric conditions; these events were seen in a negative light and presented as reasons not to participate. Male non-users also mentioned salient events acting as barriers to screening; these were generally unrelated to medical matters or illness (e.g. relationship breakdown, child custody battle).

Uniquely female non-users had poor trust in the medical profession, particularly their local hospital, and this influenced their decision not to take part. Some male non-user had issues with the environmental context, specifically delivery of mail, implying the screening invitation did not reach them.

Female non-users' attitude to FIT test materials was often negative and related to the sampling kit (e.g. catching of the stool using the paper provided, using the sampling stick) and packaging for storing the sample in their refrigerator (e.g. concerns about food contamination). Male non-users had few or no issues with the resources and material.

Beliefs about capabilities

Screening users

Both male and female users had strong confidence in their ability to do the test, describing how they carefully followed the test instructions and pointing out "it's not rocket science".

Screening non-users

Male non-users generally believed they would have had no problems conducting the test despite not participating. Female non-users raised several issues impacting on their perceived ability to carry out the test, including an inability to deal with faecal matter and lack of confidence in sampling stool with the equipment provided. Others suggested that they felt confident to recognise illness in themselves observing that they did not participate in screening because they felt they were not ill or that they had no bowel symptoms; several made statements such as "you know your own body" and "if it's not broke don't fix it".

Beliefs about consequences

Screening users

Both female and male users were very positive about the implication of a colorectal cancer diagnosis, often stating that they considered that early detection is the key to successful treatment.

Screening non-users

Both female and male non-users were generally negative about the implication of a colorectal cancer diagnosis. Many female non-users discussed undergoing surgery and the potential need for a colostomy bag in negative terms. Male non-users often held fatalistic beliefs that a diagnosis inevitably resulted in death.

Social influences

Screening users

Male users spoke about the positive influence of female partners in their decision to participate. Female users discussed social influences outside the family on their

screening participation including the impact of media campaigns for other cancer screening and quitting smoking.

Screening non-users

Female non-users raised a range of social influences which were generally negative and influenced their decision not to participate in screening (e.g. a neighbour who experienced colonoscopy-related complications, lack of encouragement from one's GP, discouragement by one's mother). While there were fewer social influences on male non-users' screening decisions, some discussed a female relative's unsuccessful attempt to encourage them to participate.

Emotions

Screening users

Male and female users spoke of their decision to be screened with positive emotional affect feeling it was a "brilliant idea". Although male users sometimes mentioned fear of cancer and embarrassment (with respect to the test), these did not inhibit their participation. Instead fear of cancer was a catalyst to screening, providing "peace of mind" in knowing that one has a "pretty good chance of not getting it".

Non-users

Female non-users expressed negative emotions around screening including disgust (related to handling faeces or storing the sample in the fridge), anger (timing e.g. receiving test while grieving a spouse's death) and fear (of cancer). Some female

non-users described emotional burnout due to other conditions leaving them emotionally unequipped to deal with a potential colorectal cancer diagnosis, leading them to decide not to participate. Male non-users expressed negative emotions relating to a fear of cancer, and dying (considered as potential consequences of screening) influencing their decision not to participate.

Knowledge

Screening users

Generally female users considered their risk of developing colorectal cancer as low, based on their family history of the disease and lifestyle (which they considered "healthy"). Some male users considered they had low risk because they had previously had a colonoscopy (either having a negative result or polyps removed) and therefore were in no immediate danger or because they had a healthy diet and lifestyle; others considered that they had high risk because of other gastrointestinal conditions (e.g. Crohn's disease). Overall, users had a very considered view of their colorectal cancer risk and felt screening participation would sustain a low risk or reduce a high risk. Male and female users often knew other people with colorectal cancer and this motivated them to participate in screening.

Screening non-users

Female non-users generally believed that their risk was low, mainly because they had no family history or symptoms of the disease (generally understood as frequent bowel motions). This perceived low risk led them to believe they did not need to be screened. Male non-users generally stated they did not know their risk

of developing colorectal cancer and were often unsure if they knew anyone with colorectal cancer.

Female non-users were often unclear about the screening procedure, and sometimes described having not read the information sent with the test kit. Male non-users stated that they were clear about how the test was carried out but upon discussion several had misunderstood how to complete it.

5.4 Discussion

We used qualitative methods to explore influences on males' and females' decisions to participate in FIT-based colorectal cancer screening. Considering FIT based screening is increasingly being used in population-based programmes, and that uptake is variable (19%-76% in population-based programmes, average 44% (15)), this study provides valuable information on factors influencing non-participation, examining these differences by gender. Six TDF domains emerged as influencing individuals' decisions on FIT-based screening participation. Although all of these domains were evident for users and non-users, issues within domains differed between groups, or the same issues played out differently in the two groups and sometimes by gender.

Negative attitudes, beliefs and emotions, pervaded decisions of non-users, while positive attitudes, beliefs and emotions were evident among users. Negative attitudes are associated with lower colorectal cancer screening participation. (25, 26) Our study found differences in these attitudes and beliefs by gender especially

among male and female non-users. These included differences in salient events (medical matters in females and non-medical matters in males); response to materials and resources (test kit, storage and faecal sampling in females; non-test related factors in males); perceived consequences of screening and diagnosis (males' fatalism); and social influences (negatively impacting on females' decisions, but less apparent in males).

Fear of cancer and fatalistic beliefs result in low adherence to screening recommendations (27) but fear may have different effects on screening decision-making around participation (28); this has not been explored by gender. In our study, although male users had some fear around a cancer diagnosis, this did not impede participation whereas in non-users fear was an impediment to screening. Fatalism has been associated with poor screening uptake (19,29–31) and those with greater fatalistic beliefs are more likely to believe they have a greater risk of cancer and that it is a more severe disease. (31) Where our study extends these is that we found fatalistic beliefs were present among male non-users only and influenced their decision not to participate.

Non-users, particularly male non-users had poorer knowledge of colorectal cancer than users and less often knew of others with cancer. Knowledge about cancer generally, and knowing someone with colorectal cancer, is positively associated with screening intention and participation (25,32,33) while low health literacy has been identified as influencing non-participation. (34) Our findings suggest that health literacy and social supports which provide opportunities to learn about illnesses or screening may be especially poor among male non-users thereby

influencing non-participation. Von Wagner et al, have suggested the use of a wider range of communication strategies in raising awareness of screening (35) and we concur with this.

Disgust influenced females', but not males', decisions to participate in screening. Different forms of disgust, such as trait disgust (the stable tendency to experience disgust) and state disgust (current emotional experience), might influence particular types of decisions such as taking part in screening. A recent study found that while females had higher scores for both forms of disgust, between-gender differences were not significant, but the authors acknowledged methodological limitations. (36) There is a need for research identifying how screening information could address anticipated disgust (36,37) and our finding suggests this should be considered with gender differences in mind.

There were few differences between male and female users in influences on screening decisions, but female relatives often influenced male users' decisions to be screened but this influence did not operate in the other direction. Spouses play an important role in colorectal cancer screening decision making; (38,39) and women have been described as the guardians of men's health (40); our study appears to be the first to show that this positive influence operates only for men. Among male non-users, while social influences were fewer, females relatives had sometimes attempted to influence them, albeit unsuccessfully. Further investigation of the influence of females on male screening decision-making is warranted.

Male non-users were less clear about their non-participation than female non-users, citing external circumstances or that they had forgotten or didn't have time. Those who cited external circumstances or forgetting as reasons for non-participation could have been masking their true reasons. Elsewhere it has been reported that unscreened males often procrastinated about screening, being vague and emotionally distant around screening decisions. (19) In our study a small number of male non-users revealed that they unconsciously resisted doing the test due to an underlying fear of the potential outcome of screening. Further investigation on resistance to screening in males is warranted.

This is the first study to employ the TDF within a qualitative study investigating influences on FIT-based colorectal cancer screening decisions. Although interviewees were recruited from a population-based screening programme, this operated in a specific area in one city and it is possible that themes/influential domains may not generalise to other settings/populations. Our sample was drawn from a screening programme which had finished two years prior to recruitment and interviewees may have had difficulty with recall, although we provided recall aids. One (male) interviewer conducted all interviews and while this provided consistency across interviews, it is possible that the interviewer's gender influenced interviewees' responses. Finally, while we reached saturation of themes across the entire dataset, and in all strata except male non-users, the relatively small number of non-users who were interviewed is a limitation. Recruitment of non-users was challenging: 550 individuals were approached in order to obtain interviews with19 people. It is possible that if more non-users had

participated further domains might have been identified as influencing screening decisions.

5.6 Conclusions

Our study provides novel information on influences on FIT uptake in men and women. Further investigation is required of whether and how the influences identified in this study operate independently and together at the population-level. Our findings may be used to inform the development of gender-specific interventions designed to improve uptake in FIT-based screening programmes. Moreover, the opportunity exists, within Ireland at least, where colorectal cancer screening is relatively new, to open a national discussion on the benefits of FIT-based screening, tackling the issues raised in this study and ultimately seeking to improve screening participation in both genders.

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Table 3.1: Illustrative quotes for domains potentially influencing screening decisions in users, by gender

Domain	Female compliers	Male compliers
Environmental context and resources	She had bowel cancer. Well, her bowel burst, actually, she's lucky to be alive. I thought, oh no, I need to get this done, because there's slight changes, do you know.(P-9)	And certainly in light of the two guys, friends of mine who are in trouble now. So I would certainly be very conscious of it.(P-28)
Beliefs about capabilities	Well, I thought so. I mean, it's pretty simple to do, just take the little stick and... It's not exactly rocket science.(P-7)	It was easy enough, yeah. Yeah, you just prepare whatever you have to do upstairs and do it.(P-32)
Beliefs about consequences	But I always feel that if you had to get a cancer, it wouldn't be one of the worst *[colorectal cancer]*, because it is treatable, and if it's caught in time I think you have a better chance than you have if you got pancreatic cancer.(P-3)	If they got it in time, if they were screening, and all that, that's the way I believe in it. Well, it's like anything, I suppose, if you get it in time.(P-26)
Social Influences	If I came to a bowel cancer awareness week or breast cancer or bowel cancer or whatever, it would make me think, and it's "oh I must follow up on that and have all that checked out for myself".(P-3)	She nagged me into it [female spouse], so I did it.(P-35)
Emotions	I thought brilliant....Great idea. Any of those tests for prevention, I would say, is a great idea.(P-1)	The more people you've met or have known that have had cancer, and the closer you are to getting it, the more frightening it becomes, especially when people die, obviously.(P-29)
Knowledge	I suppose it's one of the cancers I would think, no, you won't get that...it's just maybe to do with diet and lifestyle, is a lot to do with it probably.(P-6)	Well, at the moment, after doing this *[colonoscopy]* I think I'm okay.(P-29)

Table 3.2: Illustrative quotes for domains potentially influencing screening decisions in non-users, by gender

Domain	Female non-compliers	Male non-compliers
Environmental context and resources	I got it the morning after my young fellow nearly died the night before and I just... I'm sick of hospitals...and it was all bowels .(P-19)	So I just kept putting it off. I mean, in and out of the courts for the last… I mean, I'm going to the High Court now *[custody battle]*. So I've been down the courts for the last 12 years.(P-45)
Beliefs about capabilities	Well, when I saw what you had to do, I couldn't cope with that *[faecal sampling]*.(P-15)	Yeah...I'd do it myself now. I've no problem doing it now. (P-39)
Beliefs about consequences	It'd probably be fairly invasive and end up with bags and all sorts of things.(P-18)	I'd say they'd be dead. Because there's no cure for cancer is there, not that I know of anyway.(P-47)
Social Influences	Well, it was my mother, when I got the letter my mother said, "Throw that in the bin, you don't want to know anything about yourself."(P-16)	And she *[wife]* said to me, "Did you do it?" "Aye," I said. But I didn't.(P-46)
Emotions	I thought, 'I'm not doing that' *[faecal sampling]*. Yes... If it had been probably- oh God, it sounds disgusting.(P-13)	At the time it was, yeah, it was a fear of dying.(P-47)
Knowledge	That would have been on my mind, opening that pack, and looking at it and thinking, 'Well, I don't have the symptoms that [sister] had. If I have, I'll go.'(P-22)	But you wiped your bottom and you sent this piece of paper off to the...wherever, the lab.(P-40)

6 Negative emotions and cancer fatalism are independently associated with uptake of FIT based colorectal cancer screening: Results from a population based study

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6.1 Abstract

Background: Few behavioural or attitudinal factors have been identified in improving participation in population-based colorectal cancer screening. We explored knowledge and beliefs about cancer, health literacy, emotional attitudes to screening, and social influences among individuals invited to a population-based screening programme.

Methods: A cross-sectional survey of 2299 individuals (users and non-user) of a population-based FIT screening programme was conducted in the latter half of 2016. Factors of interest were explored using previously used and validated measures. The primary outcome variable modelled was uptake status (User or Non-User); multivariable logistic regression was used to estimate the odds ratios (OR) for participation.

Results: Stronger fatalistic beliefs independently predicted lower uptake (OR 0.94; 95% CI 0.90-0.98; P=0.003), while being younger and disagreeing that "cancer can often be cured" also independently influenced lower uptake (OR 0.45; 95% CI 0.24-0.84: P=0.019). Stronger negative emotional attitudes to screening independently predicted lower uptake (OR0.83: 95% CI 0.83-0.80-0.87: p<0.001), while the influence of a partner on decision to be screened independently predicted higher uptake (OR 1.37; 95% CI 1.20-1.57: P<0.001).

Conclusion: Key barriers to uptake in FIT-based screening include cancer fatalism, the belief that cancer cannot be cured and negative emotional attitudes to the FIT test, while the influence of a partner facilitates use. Challenges now exist in how to improve uptake by exploring if these negative beliefs and emotions are modifiable in terms of intervention development. An additional challenge lies in improving uptake among those not in co-habiting relationships.

6.2 Introduction

Colorectal cancer is the second most common cancer diagnosed in females and third most common in males (1). Rates of the disease are highest in the most developed countries (2) and, both in more and less developed regions both incidence and mortality rates are higher in males (1). Colorectal cancers develop from adenomas polyps; polyps are usually asymptomatic in earlier stages (6,7) and transition to invasion often takes more than 10 years (3–5) (6,7). Screening for adenomas or early cancers has proven efficacious in reducing cancer incidence and mortality (3,5,8,9) and several screening tests exist. Current colorectal cancer screening guidelines recommend population-based screening in those aged 50 or over using invasive tests (colonoscopy or flexible sigmoidoscopy) or in those aged 50-74 using non-invasive tests gFOBT or FIT (10,11). In Europe, screening programmes tend to employ non-invasive methods (12,13) and guidelines in recent years have recommended programmes move from gFOBT to FIT as the latter has higher sensitivity and specificity and does not require dietary restriction (10,11), Indeed, FIT is now recognised by most countries as the screening test of choice and the marker against which new tests should be compared and assessed (14).

In order to achieve health gains at the population-level, colorectal cancer screening programmes require high uptake (10,15,16). FIT-based screening achieves higher uptake than screening using other tests (17,18) yet uptake is suboptimal overall, and significantly lower among males and lower socioeconomic groups (19,20). (In)equity in screening, if left unchecked, may lead to further disparities in health outcomes among those who are most at risk.

Therefore, while improving overall uptake is important, focus is also needed on reducing differentials in uptake (15,21). While many strategies to improve uptake have been tested (22), most have had no effect on uptake. This suggests that greater understanding of why people (and particular subgroups of people) decide to participate or not in colorectal cancer screening would be valuable in informing the content for future interventions.

Evidence relating to reasons for non-participation with colorectal cancer screening is very limited, particularly for FIT. In a recent systematic review of FIT screening uptake, we found that while males were significantly less likely to take part, the drivers of lower uptake did not appear to be related to screening programme design or organisation (19). Our subsequent qualitative research suggested that negative beliefs about cancer and negative emotional attitudes towards screening, poor knowledge about cancer and health literacy, and social support, may play a role in low uptake overall, and especially among males (23), but whether these factors are related to uptake of FIT-based screening at the population-level is unknown. We undertook this population-based study to quantify associations between uptake of FIT-based colorectal cancer screening and (i) colorectal cancer knowledge and health literacy, (ii) beliefs about cancer and emotional attitudes to cancer and FIT based screening and (iii) social influences. Our secondary aim was to determine whether these associations differed in males and females.

6.3 Methods

Study population.

The study setting was the Tallaght region of Dublin, which has a population of 70,000 and is one of the most disadvantaged areas of the country (CSO, 2011). The Tallaght Hospital/Trinity College Dublin Colorectal Cancer Screening Programme (TTC-CRC-SP) was a population-based screening programme and offer two rounds of screening using FIT during 2008 to 2012, (round 1: 2008-2010: round 2: 2010-2012). Individuals aged 50-74 were identified through seven primary care practices in Tallaght. Participants with a severe inter-current illness precluding bowel preparation or colonoscopy were excluded, as were those who had undergone a colonoscopy within the previous 2 years(24). 9785 individuals were invited to participate in screening. These individuals were sent an invitation letter which also contained a FIT test kit. To participate, they were required to provide a single faecal sample which they posted to the laboratory using a prepaid envelope. An information sheet on colorectal cancer was also included in the initial invitation and all invitees received identical information. A reminder at 12 weeks was sent to those who did not respond. Upon commencement of round 2, individuals who had left the catchment area after round one, had been diagnosed with colorectal cancer or were deceased were excluded; everyone else was invited to take part (irrespective of whether they had participated in round 1) A positive result on the FIT was followed up with a diagnostic colonoscopy. Participation in screening was free, as were follow-up investigations, procedures and treatment if cancer was detected.

Study design

In September 2015 we selected a sample of individuals from the TTC-CRC-SP database to be invited to complete a questionnaire. The database was stratified by

participation status and sex. Non-participation (henceforth "non-users") was defined as having not taken part in either screening round and participation (henceforth "users") was defined as taking part in either or both rounds of screening. We invited the entire sample of non-users (n=3738; 1830 males & 1908 females)) to take part in the study. We stratified the user sample by sex, randomly sorted each group then selected 1830 men and 1908 women (the same numbers as in the non-users groups) to participate in the study . The non-user and users were mailed the questionnaire, a participant information leaflet and a prepaid reply envelope. Reminders were sent at 3 and 6 weeks (with a second copy of the questionnaire at 6 weeks) to those who had not responded. The study was approved by the Research Ethics Committee of St James/Adelaide &Meath Hospital incorporating the National Children's Hospital (REC Reference 2013/12/05).

Questionnaire

The questionnaire (supplementary material – appendix C) was developed to explore factors impacting on uptake and was informed from our previous exploratory qualitative study (23). Information was collected on age, highest level of education completed, employment status, medical card status (those on reduced means (i.e. below a certain income threshold) are provided with a medical card which entitles them to access health care, including primary care, in the public health system, free at the point of delivery), private health insurance, smoking status and self-rated health (25). The National Cancer Registry geocoded all addresses in the screening database and an area level deprivation score (26) was assigned to each individual (20).

Measures

Cancer knowledge and health literacy

To gauge cancer knowledge participants were asked two questions: (i) if they knew of anyone who had been diagnosed with bowel cancer and (ii) if they knew anyone who had been diagnosed with any cancer (27). Response options for both questions were "Yes me", "Yes someone close to me", "Yes me and someone close to me", "Yes, but prefer not to say" and "No" with responses collapsed into two categories (No knowledge of someone or self with cancer (No) or knowledge of other or self with cancer (all other responses)). Health literacy was measured using a single item measure (28) which has demonstrated ability to detect inadequate health literacy in screening populations (28–30). Respondents were asked "how confident are you filling out medical forms by yourself?" with responses on a five point scale ("Extremely", "Quite a bit", "Somewhat", A little bit" and "Not at all"). Responses were combined to measure inadequate and adequate health literacy (Inadequate: "Somewhat", "A little bit" and "Not at all").

Beliefs about cancer and emotional attitudes to cancer and screening

Beliefs about cancer were measured using six separate single item statements (three negatively framed and three positively framed) from the Awareness and Beliefs about Cancer (ABC) questionnaire (27) (supplementary material); response options on a four point Likert-type scale (from "strongly agree" to "strongly disagree") were reduced to two categories ("agree" or "disagree"). Fatalistic beliefs about cancer were measured using the Powe Fatalism Inventory which was amended to be specific to bowel cancer (31) and contained fifteen

items with two response options ("Agree" or "Disagree"). Items responses were summed. Higher scores indicated greater cancer fatalism (scale ranging from 0-15). Internal consistency here was adequate (α =.86). Negative emotional attitudes toward the FIT screening test were assessed using a five item scale developed by Smith et al, which includes items on disgust, tempting fate, embarrassment, worry and being afraid (32). Responses were on a four-point scale from "strongly agree" to "strongly disagree" with higher scores (ranging from 5-20) indicating more negative emotional attitudes. Internal consistency was adequate (α =.85). Three separate aspects of cancer fear - cognitive , affective and psychobiologic - were measured using questions adapted by Vrinten et al, all of which were measured on a five point Likert type scale (strongly agree to strongly disagree)(33). We collapsed the strongly agree and strongly disagree responses to give three response categories (Agree, Disagree or Uncertain).

Social influences

Social influences were measured in three ways. Firstly, four questions on perceived beliefs about key references' (two questions on partner's and two questions on GP's) attitudes towards colorectal cancer screening (34,35) were included. Responses were summed to give an aggregate score from 1-4 (strongly agree to strongly disagree), with higher scores equating to greater social influence. Our primary interest was in the influence of a partner on screening decision so we also ran separate analysis assessing the influence of a partner alone. Internal consistency was adequate (Partner and GP α =.86; Partner alone α= 0.82). We used the Oslo Social Support Scale to measure the extent of social support (36). Responses were summed and categorised as poor, moderate or strong social support, as recommended (36). Internal consistency was low (α

=.56). We also included relationship status (married/cohabiting or not) as the third measure.

Statistical analysis

Characteristics of users and non-users were compared using chi-square tests for categorical variables. Age at the time of the survey was collected further grouped into two categories ("64 or less" and "65 or more"). Continuous scale variables were summarised using means and standard deviation, and differences between users and non-users and males and females tested using the Mann Whitney U test. Differences between categorical variables in users and non-users were tested using chi square tests. We then developed a multivariable model for factors associated with uptake. This was done in three stages. In stage 1 we established a "base model" of socio-demographic factors. Candidate variables for inclusion in this model were socio-demographic factors previously shown to be associated with uptake of FIT or FOBT both in this population and elsewhere (20,37) (i.e. age, sex and deprivation) and other available demographic and health variables (education, employment status, medical card status, private health insurance, smoking status and self-rated health). These were each tested individually for associations with uptake and those which were significant were fitted simultaneously. Variables which remained significant (likelihood ratio $p < 0.05$) when mutually adjusted were retained in the base model. In stage 2 we fitted three separate blocks of explanatory variables (Block 1; cancer knowledge and health literacy, Block 2; beliefs and emotions and Block 3; social influences) to the base model. Within each block, individual variables were added to the base model separately. In stage 3, variables which were significant in stage 2 were

added to the base model to build the final multivariable model. Variables were included in the final multivariable model if the p value from the associated likelihood ratio test (LRT) was <0.05, and the variable was not collinear with another in the model. Akaike information criterions (AIC) and Bayesian information criterions (BIC) were used to inform choice of variables in the final model. The final model had adequate fit, based on the Hosmer & Lemeshow test. Variance inflation factors and tolerance of the final model were above 0.1 and less than 10 (38). We then tested for interaction between sex and the explanatory variables which remained in the final model by fitting cross-product terms, one at a time. We also re-ran the final model after stratifying the dataset by sex. All analysis was carried out using Stata 14.

6.4 Results

Response rates

Of the 7476 individuals invited to participate in the study, 31% (n=2299; males, n=1198; females, n=1101) returned a completed questionnaire. The response rate among FIT screening users was 53% (n=1988; males, n=1014(55%); females, n=974 (51%): P=0.139) and non-users was 8% (n=311; males, n=184 (10%); females, n=127 (7%): P<0.001)

Stage 1: Base model

There was a significantly greater proportion of male non-users compared to female non-users (males: 59% vs females: 41%; P=0.007). Compared to users, significantly greater proportions of non-users were resident in more deprived areas (52% of non-users were resident in the very disadvantaged and

disadvantaged areas compared to 35% of users; P<0.001), and a significantly greater proportion of non-users were aged under 64 (<=64: 60% of non-users vs 49% of users; P<0.001) (Supplementary table 3.1). No other factors (education, employment status, medical card status, private health insurance, smoking status and self-rated health; data not shown) differed significantly between users and non-users.

Three socio-demographic variables were significantly associated with uptake, once mutually adjusted - sex (OR males: 0.68; 95% CI 0.53-0.87; P=0.002), deprivation (Test of trend for increasing affluence, OR: 1.47; 95% CI 1.28-1.69; P<0.001) and age group (OR 1.01; 95% CI 1.00-1.01; P<0.001). These comprised the base model.

Stage 2: Univariable associations and minimally adjusted models

Block 1: Knowledge and health literacy

In univariate analyses, knowledge and health literacy variables did not differ by uptake status overall. However this masked significantly higher proportions of inadequate health literacy among female non-users compared to female users (Supplementary table 3.1).

Knowledge or health literacy did not influence uptake when fitted separately to the base model (Table 4.1).

Block 2: Beliefs and emotions

In univariate analyses, for measures of beliefs about cancer, higher proportions of non-users disagreed with two positive statements and higher proportions of non-users agreed with all negative statements (supplementary Table 3.1). Cancer

fatalism was also significantly higher among non-users (mean 4.15; SD= 3.07) compared to users (2.90; SD=3.81: P<0.001) (Supplementary Table 3.2). There were no differences between non-users and users in fear related to cancer (cognitive, affective or psychobiologic). In relation to emotional attitudes to the FIT test non-users had significantly higher mean scores indicating more negative emotional attitudes to screening (Supplementary Table 3.2).

When fitted individually to the base model, five beliefs about cancer influenced uptake. There were significantly lower odds of participation if in disagreement with two positive statements ("These days many people with cancer can continue with normal activities" (47% lower) and "cancer can often be cured" (50% lower)) and significantly higher odds of participation if in disagreement with all three negative statements ("the treatment is often worse" (40% higher),"they would not want to know if they had cancer" (66% higher) and "cancer is a death sentence" (47% higher)) (Table 1). For each unit increment in cancer fatalism the odds of participation decreased by 9% when fitted to the minimally adjusted base model.

Those with stronger negative emotions related to screening had significantly lower odds of participation in the minimally adjusted base model with a 16% decrease per unit increase in negative emotional attitudes (Table 4.1).

Block 3: Social Influence

In univariate analyses, there was a significant difference in the influence of a partner (or partner and GP (data not shown)) on the decision to be screened with higher mean scores (i.e. stronger partner influence) among users compared to non-users (Supplementary Table 3.2).

When added to the base-model, relationship status was significantly associated with non-use among those who were not in a co-habiting relationship (32% lower odds of participation). The social influence of a partner scale also influenced uptake in the minimally adjusted base model with each unit increase in the influence of a partner resulting in a 30% increase in the odds of participation (Table 4.1). The Oslo Social Support scale was non-significant.

Stage 3: Final multivariable model

The variables in the final model were sex, deprivation, fatalism, emotional attitudes to screening, influence of a partner and a term representing an interaction between the belief that cancer can be cured and age (Table 4.2).

The odds of screening uptake were 40% lower in males than females (OR 0.58: 95% CI 0.43-0.79; P<0.001) (Table 4.2). The odds increased by 30% for each unit increment in affluence (test of trend OR, 1.30: 95% CI 1.10-1.53; P=0.002). For each one unit increase in cancer fatalism score the odds of uptake decreased by 6% (test of trend OR, 0.94: 95% CI 0.90-0.98; P=0.003). For the composite variable of age and the negative cancer belief that "cancer can often be cured", compared with those aged 64 or less who agreed with the statement, there was a 66% lower odds of participation only among those aged 64 or less who disagreed with the statement (OR, 0.45: 95% CI 0.24-0.84; P=0.019). With the inclusion of this factor co-linearity with the fatalism index did not destabilise the model. Stronger negative emotions about screening were significantly associated with lower uptake with a 17% decrease in the odds of uptake for each unit increase in negative emotional attitudes to screening (test of trend OR, 0.83: 95% CI 0.80-0.87: P<0.001). In addition, for each one unit increase in the influence of a

partner (social influence), the odds of uptake increased by 37% (OR 1.37; 95% CI 1.20-1.57; P<0.001).

Secondary analysis: factors associated with uptake by sex

When the final model was stratified by sex, the association between uptake and affluence was somewhat stronger in females than males (43% in females and 20% in males for each unit increase in affluence) (Table 4.3). The estimates for partner influence was slightly greater in males than females but the interaction with sex was non-significant (Influence of a partner*sex; p (interaction) = 0.996). The strength of the association with negative emotions and uptake was similar in males and females, and the test of interaction was not significant (Screening emotions*sex; p (interaction) = 0.643). Cancer fatalism was also similar in males and females when stratified and the test of interaction was not significant (cancer fatalism*sex; p (interaction) =0.859). The estimate of the odds of participation in males aged 64 or less who disagreed that "cancer can often be cured" decreased slightly in males, however there was no significant interaction between the composite variable and sex (Age & Belief cancer can be cured*sex; p (interaction) =0.0.384).

6.5 Discussion

Screening uptake for colorectal cancer is relatively low in most (if not all) settings (19) and often below levels achieved in other established population based cancer screening programmes (21). We conducted this study to inform the development of strategies to improve uptake of FIT-based colorectal cancer screening and, indeed, our study presents new evidence on factors influencing FIT-based screening uptake. Weller et al have pointed to the need to focus on

areas of uncertainty and unrealised potential, while taking into account the complexity of factors associated with screening uptake (15). In this regard obtaining data on such a hard to reach group is of great value in attempting to understand low uptake and this is enhanced through the verification of participation through screening records as opposed to self-reported screening. In attempting to understand what factors may be a focus for interventions aimed at increasing uptake our study marks a starting point for FIT based interventions. Our study shows significantly lower uptake among those with more negative beliefs about cancer (in particular fatalistic beliefs), and among those with more negative emotional attitudes towards FIT-based screening. In addition the influence of a partner on ones decision to be screened increases uptake.

As far as we are aware this is one of the first studies to examine the relationship between beliefs and emotions related to FIT-based cancer screening. Younger participants who disagreed that "cancer can often be cured" were less likely to take part in FIT based screening, but this was not seen in older people. Although five of the six negative beliefs remained in the minimally adjusted models only the statement "cancer can often be cured" remained in the final model. This focuses attention on those with negative beliefs about cancer and, in particular, those who disbelieve that "cancer can often be cured" require particular attention, especially in view of the fact that colorectal cancer is a highly treatable disease if detected early, which is (of course) one of the aims of screening (10). While this belief is similar to holding fatalistic beliefs about cancer we choose to keep this factor in our final model. As part of a broader set of beliefs about cancer disagreement with the specific belief "cancer can often be cured" may represent a specific belief held among non-users particularly in relation to concepts of

destiny and personal agency (39). The decision to keep this belief in the final model is further strengthened by the fact that co-linearity between this belief and the fatalism index did not destabilise the final model. Further investigation would be useful on this specific view in terms of its influence on uptake and how it may operate differently to fatalistic beliefs in non-use of screening.

Fatalistic beliefs about cancer have been found to be a factor in late stage presentation of colorectal and other cancers (40) as well as a marker of poor uptake in studies of FOBT colorectal cancer screening (31,41). This study extends this evidence and demonstrated that this association also holds for FIT-based screening. Drew et al have suggested that fatalism (defined as a belief in a lack of personal power or control over destiny or fate) constitutes a major barrier to participation in positive health behaviours, adversely affecting health outcomes, and that fatalistic ideas are potentially located within communities in economically resource constrained or more deprived conditions (42). Our study may well support this assumption being based in a highly deprived geographical area; moreover, our final model was adjusted for deprivation, so the observed effect of fatalism is independent of this. Von Wagner et al have pointed out that ill health and premature death are more common among lower socio-economic groups and may lead these groups to experience a greater sense of fatalism as a result of cancer diagnosis (43). Cancer fatalism is not well understood and studies often measure the construct differently (40,41,44). While some studies have reported some level of success in decreasing fatalism (45,46) little is known about how fatalism can be a focus of behavioural interventions aimed at increasing screening uptake (46,47). While deprivation did not attenuate the relationship between uptake and gender it would be useful to extend our analysis through the

use of mediation analysis and structural equation modelling to explore the extent to which beliefs may explain a potential association between deprivation and uptake.

A recent study among a FOBT screening population has shown that intent to take part in screening is lower among those with high emotional barriers and lower levels of education (48). Our study confirms and extends these findings by showing that these negative emotions are a barrier to actual uptake, rather than just intent, as we have verified participation through screening records.

While negative beliefs and emotions centring on the screening test, and on cancer itself, were associated with screening participation, we did not find evidence of differences in males and females in terms of the influence of these factors. This is at odds with our previous qualitative work. A possible explanation is that the negative emotions themselves may not be driving screening decisions, but rather they are driven by how people process information that presents a risk to their health, and this processing may be different in males and females. Recent research has provided some insight into how individuals may process risk information defensively, such as opting out at a behavioural or informational level, blunting, suppressing or counter arguing against such information (49,50). It has been reported also that substantial and important differences exist between knowledge, attitudes and defensive processing (primarily related to numeracy; a factor related to health literacy) (32). McQueen et al report that males in their study examining patterns of association with defensive information processing about colorectal cancer screening had significantly higher mean defence scores than females (49). This may be an explanation for why males are significantly less likely to participate in screening. Further research would be valuable to

investigate the role of defensive information processing in FIT-based screening uptake, particularly in terms of the observed associations between negative beliefs and uptake and whether its influence varies in men and women. To this end we have also collected data on Defensive Information Processing and plan to carry out this analysis in the very near future.

Marital status has been noted as a key influence on individual's health and health behaviours (51,52). A recent systematic review reported that the positive influence of a partner is the most common facilitator to health screening for males (53). It has also been reported that intention to be screened for colorectal cancer is stronger among married individuals compared to non-married individuals (54). We have also found that the influence of a partner on decision to be screened is a key influence on decision to take part in colorectal cancer screening using FIT. Elsewhere marital status and a member of the opposite sex have been shown to be a strong influence on men's decisions to seek health care (55). Within our stratified model, while significant in both sexes, the effect of the influence of a partner was greater in males than females. Jaarsveld et al have reported that inviting the two partners together for colorectal cancer screening increased attendance rates in both males and females (54). It would be useful to examine the effect of inviting partners together as this may have a beneficial effect on FIT-based screening uptake, especially among males (19). Therefore it may be useful for screening programmes to design their invitation strategies in relation to households. This aside, those who are not in a relationship have significantly lower uptake and this group warrants particular attention.

We found no evidence that either cancer knowledge or health literacy influences uptake of FIT in our population, a finding that is counter to other colorectal

cancer screening uptake research (56,57). However our results may well be null due to how we have measured health literacy. Although the measure we have used to determine inadequate health literacy has been validated elsewhere (among veterans and patients attending a primary care clinic in the US) it may not have applied well to our screening population. Using a single item question to gauge inadequate health literacy may lack sufficient sensitivity. It would be useful to use a more extensive measure in future. Given that health literacy is associated with education and socio-economic status (41,43,58), another possible explanation for our null result might be the generally deprived nature of the study population; it is possible that we may not have had sufficient discrimination in levels of health literacy within the study population to find differences. We measured knowledge of others with cancer or bowel cancer (23,59) to assess if this had any effect on uptake and found this did not influence uptake. Future studies will likely benefit from a broader investigation of cancer knowledge.

As far as we are aware, this is the first study to examine the relationship between beliefs and emotions related to FIT-based cancer screening. It is also one of the few studies to verify screening status using screening programme records rather than self-report. A limitation of the study is the low response rate of screening non-participants (8%). As our interest was in understanding reasons for non-uptake, we aimed to maximise the numbers of screening non-users responding to the survey. We therefore utilised the entirety of the sample of non-users and selected at random an equal number of users (based on sex). Given the response rate, it is likely that those non-users who took part are a selected group. However, analyses of associations between age, deprivation and sex and uptake in the survey responders produced identical patterns (and very similar risk estimates) as

when the entire screening programme dataset was analysed (20), which is reassuring. Nevertheless the low non-user response rate highlights the difficulties of involving hard-to-reach groups in screening research. Waller et have recently reported the heterogeneity of female non-participants of cervical cancer screening in the Britain, 28% of whom were unaware of screening and 15% of whom had decided not to attend (60). This would be a useful exercise to repeat in Ireland's colorectal cancer screening population.

6.6 Conclusion

Overall our study suggests that, after adjusting for socio-demographic influences, key barriers to uptake in FIT based screening include fatalistic and negative beliefs about cancer and negative emotional attitudes to the screening test; in contrast influence of a partner appears facilitate use. Future research needs to investigate influences on uptake among those not in cohabiting relationships and if negative beliefs and emotional attitudes to cancer and screening are modifiable in terms of designing interventions to improving uptake.

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Table 4.1: Absolute uptake by participant characteristics (numbers and %) and univariable and adjusted odds ratios (OR) for participation in FIT-based colorectal cancer screening with 95% confidence intervals and p values

	Total	Users		Adjusted model*			
	N	N	%	OR	95% CI		P
Base model*							
Sex							
Female	1,101	974	88.5	-	-	-	
Male	1,198	1014	84.6	0.68	0.53	0.87	0.002
Age							
<65	1133	950	83.9	-	-	-	
65+	1126	1002	89.0	1.01	1.00	1.01	*<0.001*
Deprivation							
Very disadvantaged	206	161	78.2	-	-	-	
Disadvantaged	640	524	81.9	1.17	0.79	1.74	
Marginally below average	1156	1034	89.5	2.22	1.51	3.27	
Marginally above average	241	218	90.5	2.57	1.49	4.44	
Affluent	56	51	91.1	2.67	1.00	7.13	
*Test of trend***				1.47	1.28	1.69	*<0.001*
Block 1*; Knowledge and health literacy**							
Health literacy							
Adequate	1486	1300	87.5	-	-	-	
Inadequate	753	638	84.7	0.84	0.65	1.09	0.191
Knowledge of others with CRC							
No	1499	1307	87.2	-	-	-	
Yes	733	624	85.1	1.13	0.84	1.53	0.425
Knowledge of others with cancer							
No	437	374	85.6	-	-	-	
Yes	1805	1564	86.7	0.84	0.65	1.09	0.185

*Mutually adjusted for sex, age and deprivation

** linear trend across categories

***Separately adjusted for sex, age and deprivation

Table 4.1 continued….

	Total	Users		Adjusted model			
	N	N	%	OR	95% CI		P
Block 2*; Beliefs and emotions**							
Positive belief: People with cancer can continue with normal activity							
Agree	2033	1775	87.3	-	-	-	
Disagree	148	113	76.4	0.53	0.35	0.79	0.004
Positive belief: Cancer can often be cured							
Agree	2012	1757	87.3	-	-	-	
Disagree	112	85	75.9	0.50	0.31	0.79	0.005
Positive belief: Going to doctor as quickly as possible increases survival chance							
Agree	2103	1822	86.6	-	-	-	
Disagree	85	74	87.1	1.10	0.57	2.11	0.784
Negative belief: Treatment worse than the cancer							
Agree	1128	960	85.1	-	-	-	
Disagree	995	881	88.5	1.40	1.08	1.83	0.011
Negative belief: Would not want to know I have cancer							
Agree	244	196	80.3	-	-	-	
Disagree	1913	1674	87.5	1.66	1.16	2.35	0.007
Negative belief: Cancer diagnosis is death sentence							
Agree	460	378	82.2	-	-	-	
Disagree	1726	1516	87.8	1.47	1.10	1.95	0.010
Cancer Fatalism inventory							
User	1948		86.9	-	-	-	
Non-User	293		13.1	0.91	0.87	0.94	0.000
Fear: Cognitive: Cancer is greatest health fear							
Strongly / agree	1356	1167	86.1	-	-	-	
Uncertain	483	420	87.0	1.10	0.81	1.51	
Strongly / disagree	342	302	88.3	1.15	0.79	1.66	0.395
Fear: Affective : Worry about cancer							
Strongly / agree	885	758	85.7	-	-	-	
Uncertain	453	401	88.5	1.30	0.91	1.84	
Strongly / disagree	836	725	86.7	1.06	0.80	1.41	0.649
Fear: Psychobiologic: Discomfort thinking about cancer							
Strongly / agree	1161	989	85.2	-	-	-	
Uncertain	442	387	87.6	1.21	0.87	1.69	
Strongly / disagree	576	511	88.7	1.34	0.98	1.82	0.052
Emotional attitudes to screening scale							
Users	1940		87.2	-	-	-	
Non-users	285		12.8	0.84	0.80	0.87	0.000
Block 3*; Social Influences**							
Relationship status							
Co-habiting	1720	1508	87.7	-	-	-	
Not co-habiting	556	465	83.6	0.68	0.52	0.90	0.009
Social Support							
Poor	228	193	84.7	-	-	-	
Moderate	957	828	86.5	1.26	0.84	1.91	
Strong	1066	928	87.1	1.33	0.88	2.00	
Test of trend				1.12	0.93	1.34	0.246
Social influence of partner							
Users	1769		86.7	-	-	-	
Non-users	272		13.3	1.30	1.16	1.46	0.000

***Separately adjusted for sex, age and deprivation

Table 4.2: Multivariable odds ratios (OR) for participation in FIT-based colorectal cancer screening with 95% confidence intervals and p values

	Multivariable OR	95 % CI		P
Sex				
Female	1.00	-	-	
Male	0.58	0.43	0.80	<0.001
Deprivation				
Very disadvantaged	1.00	-	-	
Disadvantaged	1.12	0.70	1.79	
Marginally below average	1.93	1.22	3.06	
Marginally above average	1.65	0.90	3.03	
Affluent	1.80	0.59	5.50	
Trend	1.30	1.10	1.53	0.002
Cancer fatalism Inventory				
1 unit increase in fatalistic beliefs	0.94	0.90	0.98	0.003
Age & Belief cancer can be cured				
0-64 Agree	1.00	-	-	
65+ Agree	1.26	0.94	1.71	
0-64 Disagree	0.45	0.24	0.84	
65+ Disagree	0.92	0.36	2.35	0.019
Emotion attitudes to screening				
1 unit increase in negative screening emotions	0.83	0.8	0.87	<0.001
Influence of partner				
1 unit increase in influence of partner	1.37	1.2	1.57	<0.001

Table 4.3: Absolute uptake by gender with the final multivariable model of odds ratios (OR) for participation in FIT-based colorectal cancer screening with 95% confidence intervals and p values stratified by sex

	Males						Females					
	Total	Users		Multivariable	95 % CI	P	Total	Users		Multivariable	95 % CI	P
	N	N	%	OR			N	N	%	OR		
Deprivation index												
Very disadvantaged	107	82	76.6	-	-	-	99	79	79.8	-	-	-
Disadvantaged	314	257	81.9	1.61	0.85	3.05	326	267	81.9	0.77	0.37	1.60
Marginally below average	616	532	86.4	1.88	1.04	3.38	540	502	93.0	2.06	0.97	4.37
Marginally above average	129	113	87.6	1.39	0.65	2.97	112	105	93.8	2.35	0.81	6.78
Affluent	32	30	93.8	5.70	0.71	45.50	24	21	87.5	0.62	0.15	2.59
Total/ Trend	1198	1014	84.6	1.20	0.97	1.49	0.092	1101	974	88.5	1.43	1.10	1.86	0.007
Cancer fatalism Inventory*												
1 unit increase in fatalistic beliefs	1,178	1000	84.9	0.93	0.88	0.98	0.013	1063	948	89.2	0.95	0.89	1.01	0.088
Age & Belief cancer can be cured*												
64 or less Agree	477	406	85.1	-	-	-	502	430	85.7	-	-	-
65+ Agree	42	27	64.3	1.01	0.68	1.49	27	21	77.8	1.76	1.08	2.87
64 or less Disagree	555	478	86.1	0.40	0.18	0.90	445	412	92.6	0.54	0.19	1.55
65+ Disagree	21	18	85.7	0.92	0.25	3.43	0.176	20	17	85.0	0.95	0.25	3.59	0.055
Negative screening emotions scale*												
1 unit increase in negative screening emotions	1164	996	85.6	0.82	0.77	0.87	0.000	1061	944	89.0	0.85	0.79	0.91	0.000
Influence of partner*												
1 unit increase in influence of partner	1,100	937	85.2	1.49	1.23	1.80	0.000	941	832	88.4	1.28	1.06	1.53	0.009

*Interactions with sex: cancer fatalism*sex; p (interaction) =0.85; Age & Belief cancer can be cured*sex; p (interaction) =0.384; Screening emotions*sex; p (interaction) = 0.643; (Influence of a partner*sex; p (interaction) = 0.996)

7 Discussion

The aim of this PhD project was to investigate uptake in FIT based colorectal cancer screening and to compare and contrast factors associated with use or non-use of FIT in males and females in Ireland. The use of a number of different methods - as part of a single project - has allowed new insights into uptake of FIT-based colorectal cancer screening. Analysis of Ireland's population based cancer registry data on colorectal cancer, a systematic review and meta-analysis, secondary analysis of a FIT population based screening dataset, qualitative in-depth interviews, and a large quantitative cross-sectional survey has provided valuable new evidence. Firstly, the work has established that colorectal cancer screening uptake is poor in Ireland (as in many settings internationally) and that there are inequalities in uptake, not only by gender (which was the primary focus of this thesis) but also by deprivation and age. Secondly, the work has identified that uptake is influenced by certain individual beliefs and attitudes, some of which may vary between men and women. This final chapter summarises and synthesizes the main findings, and the strengths and limitations of the project. Future areas of research and consideration of the implications of the work are discussed and a brief conclusion is presented.

7.1 Summary and synthesis of main findings

In Chapter 2, data from the National Cancer Registry was used to describe the epidemiology of colorectal cancer in Ireland from 1994-2010, prior to the introduction of the national screening programme, BowelScreen. Although increasing incidence of the disease was observed (mainly due to a growing population over the period) there was no increase in the age-standardised rates of the disease, consistent with stabilisation of the rates in economically developed countries (1). Importantly the case fractions of late stage colon and rectal cancer

increased over time, but 1 and 5 year survival also rose significantly over time, likely due to advances in staging, diagnostic work-up and treatment of the disease, which has observed here and elsewhere (2–4). While age-standardised mortality rates for colorectal cancer overall decreased by 1.8% annually, rectal cancer mortality rates rose in both males and females.

These trends indicated the need for an efficient and timely roll out of a National Colorectal Cancer Screening Programme (BowelScreen). However BowelScreen began roll-out using a narrow age range and the first round took longer than initially planned (5). It is unlikely that the full extent of potential benefits from the screening programme, such as altering the stage distribution of the disease and reducing incidence and mortality in the population, will be achieved.

Uptake of colorectal cancer screening differs by test modality with invasive endoscopic based screening studies often reporting lower female uptake. The systematic review and meta-analysis in Chapter 3 provides evidence of low uptake overall, and significantly lower uptake among males than females, in non-invasive FIT-based colorectal cancer screening programmes internationally. 19 studies were included in the review; these revealed that, on average, uptake was 44% (95% CI 43.9%-44.2%) internationally and this was slightly lower when excluding non-population based studies (43%; 95% CI; 42.4%-42.8%). Random effects meta-analysis revealed males were 16% (95% CI0.75-0.95: P<0.001) less likely to participate in FIT based colorectal cancer screening, and this was statistically significant. Lower uptake in males persisted across subgroup analyses by study design, study setting, and screening organisation factors (methods of invitation,

number of samples, age-range of screening, recommendations and reminders). This study provided – for the first time – clear and comprehensive evidence of the disparity in uptake of FIT-based colorectal cancer screening in males and indicated that this disparity is not as a result of programme design or organisational factors. This demonstrated that there is a need to seek explanations for lower uptake among males, and indeed lower uptake overall.

Following from this, the next step was to identify levels of uptake of FIT-based screening in Ireland, and whether these varied by sex after other socio-demographic factors often related to uptake are taken into account. The Tallaght/ Trinity College Colorectal Cancer Screening Programme (TTC-CRC-SP) was a biennial population-based FIT screening programme conducted over two rounds during the periods 2008-2010 and 2011-2012 and prior to the introduction of national screening. Having accessed the TTC-CRC-SP for the qualitative study we investigated the effect of sex, age and deprivation status on uptake within the entire population of the screening programme and this is reported in chapter 5. The National Cancer Registry geo-coded individual's addresses allowing a deprivation index (and category) to be assigned to each person. Overall uptake was 60% over the two rounds of the study. The results show that participation was significantly lower in males (multivariable RR=0.96: 95%CI 0.95-0.97) and generally increased with increasing age. The conversion of the odds ratio reported in the systematic review to a relative risk also shows that our results are largely in line with international studies on FIT based uptake. In addition deprivation was strongly associated with participation with a 26% difference in uptake (multivariable RR=1.26: 95% CI 1.21-1.30) between those in the most deprived areas compared to those in the most affluent areas. The effect

of sex on uptake was not moderated when adjusted for deprivation or age providing new evidence that sex is an independent predictor of uptake in Ireland, as well as providing evidence for the first time in Ireland that deprivation is also an independent predictor of uptake.

The final two elements of the PhD sought to identify and investigate what influences uptake and to determine whether these vary in men and women. Chapter 4 follows on from the systematic review in investigating factors associated with low uptake in males and females. By accessing a stratified sample (male and female users and male and female non-users) within the TTC-CRC-SP we were able to explore influences on individuals decisions associated with uptake through qualitative methods. Employing the Theoretical Domains Framework (TDF) as a means of guiding the design and analysis of the study, 47 people, 19 (10 males and 9 females) of whom were screening non-users, took part in an in-depth semi-structured interview. The study is the first to provided valuable in-depth data regarding what influences people's decisions to take part, or not, in FIT-based population-based screening. The TDF is increasingly being recognised as a leading framework for the identification of influences on behaviour and this study was the first to use it as a means of understanding what influences individuals to participate in colorectal cancer screening.

Six TDF domains were identified as influencing interviewees' decisions on participation in FIT-based screening: 'environmental context and resources', 'beliefs about capabilities', 'beliefs about consequences', 'social influences', 'emotions' and 'knowledge'. Crucially, while evident in both users and non-users, these domains

did not all influence uptake in the same way in males and females. Negative attitudes and emotions towards screening and cancer dominated non-user decision-making but differed by gender. Fatalism was particularly evident in male non-users while female non-users had particularly negative emotions towards colorectal cancer screening including disgust, anger and fear. Fear was also evident among males but acted as a catalyst in users and an impediment in non-users. Social influences on decision to take part in screening, such as the influence of a partner, were strong in male users (less so in male non-users) but other influences among female non-users (other family members and lack of influence of GP) negatively impacted on participation. Knowledge also differed with male non-users having poor colorectal cancer knowledge, often not knowing of others with cancer, in contrast to both male and female users. Female non-users often believed that they did not need to take part in screening because they had no family history of colorectal cancer, or indeed any symptoms of the disease.

The final study investigated whether the potential influences on screening uptake identified in the qualitative study were associated with uptake at the population-level. For this a quantitative study was designed and this is described in chapter 6. We carried out a cross-sectional survey sampling 7476 individuals (with equal numbers of users and non-users) in the TC-CRC-SP database in the latter half of 2016. We achieved a 31% response rate overall (n=2299); 53% among users and 8% among non-users. In this analysis we focused on three areas; i) colorectal cancer knowledge and health literacy, (ii) beliefs about cancer and emotional attitudes to cancer and FIT based screening and (iii) social influences. In multivariable analyses, stronger cancer fatalism and a particular disbelief among younger people

that “cancer can often be cured” were independently, and significantly, associated with lower uptake. Those with stronger negative emotional attitudes were also significantly less likely to take part in screening, while the influence of a partner on the decision to be screened was significantly associated with higher uptake. However evidence of differences in factors influencing male and female participation in screening was not found. The results of this study provide evidence of key barriers to uptake in FIT based population-based screening. As far as we are aware, this is the first study to examine the relationship between beliefs and emotions related to FIT-based cancer screening and for the first time in Ireland provides evidence of what may be key barriers to uptake which are potentially modifiable and therefore possible targets for intervention development.

7.2 Strengths and limitations

The strengths and limitations of the individual studies have been discussed in the relevant chapters. This section summarise these limitations and provides and overview of the limitations of the thesis overall.

The main limitation of this PhD project lies in the population in which the fieldwork was conducted, namely Tallaght, a specific large urban town characterised by high levels of deprivation within county Dublin. Being urban and more deprived mean that our results may not be generalizable to other settings or populations. Given that deprivation is associated with uptake we would expect uptake in the TTC-CRC-SP to be lower than the national screening programme but this is not the case. The pattern of uptake in males and females is similar to that observed in the national screening programme. Living in a rural area has been associated with lower uptake

of colorectal cancer screening(6) and therefore our study may differ on this basis, being primarily urban. While the TTC-CRC-SP is similar in design to the national screening programme several differences do exist. Invited participants in the national programme need to make contact to request a screening test kit, while in the TTC-CRC-SP the kit was sent with the initial invitation, and one would expect higher uptake in the latter instance. In addition the national screening programme requires a single sample for a successful test while the TTC-CRC-SP required two samples on consecutive days and one would expect lower uptake in the latter instance. The TTC-CRC-SP was also endorsed by the invitees GP and this is not the case in the national screening programme, however our systematic review would suggest that this is not important in terms of differences in male and female uptake. However given that this was the first and only population to be provided with free FIT based-colorectal cancer screening in Ireland it is nevertheless a valuable population in which to assess uptake.

A further potential limitation is that the fieldwork in this thesis was carried out among people who had completed screening two years prior to recruitment of screening invitees. This may have resulted in difficulty for participants in recalling the experiences and decisions they made in relation to taking part in the screening programme. However had anticipated this and therefore provided recall aids, both within our in-depth interviews (chapter 4) and within the cross-sectional survey (chapter 5), which included images of the screening test kit.

Saturation of data was achieved in all but one of the strata within the qualitative study sample and this was among male non-users (chapter 4). This was due the

difficulty of recruiting non-users in the study. We invited 50 users to achieve 28 user participants, while inviting 550 non-users to recruit 19 non-user participants. This highlights the difficulty of recruiting non-users in screening uptake research. A €50 gift voucher was offered as a monetary incentive to participate and we informed potential invitees we would reimburse any travel expenses they may incur, although we carried out all interviews at participants homes at their request. It is possible that if we had succeeded in recruiting greater numbers of non-users, especially among males, then we may have identified further domains that potentially influence screening uptake. In this regard the influences on non-use in screening in those non-users who agreed to participate in an interview may well be different from those of non-users who did not take part in an interview. The screening population from which we drew our sample operated in a specific area of Dublin as described above, and this may potentially mean that the identified domains influencing uptake may not be generalisable to other settings or populations, for instance in a rural population or more or less deprived populations.

As within our study in chapter 6, our population-based cross-sectional survey also had a low response rate from screening non-users. While utilising the entire sample available to us we had a low response from non-users. Given this low response rate it is likely that our sample of non-users are a selected group. However we carried out similar analysis of associations between sex, deprivation and age, which was employed in our study of the entire screening population in chapter 4, and this produced identical risk estimates for uptake and this is reassuring. Once again however this highlights the difficulty of recruiting non-users in screening research. Issues may also exist in how we measured health literacy in our study. Health

literacy has been associated with lower uptake in some colorectal cancer screening populations(7–9) and our finding is contrary to those. We used a single item measure which has been validated in other populations (among veterans and patients attending primary care clinics in the US(10,11)) but it may have lacked sufficient sensitivity, or may not work in other settings. We may also have lacked sufficient discrimination to detect health literacy differences within our population due to the deprived nature of our sample and the fact that health literacy is associated with markers of socio-economic status(12–14).

Despite the limitations the thesis has several strengths. The fieldwork undertaken accessed the only available colorectal cancer screening population in Ireland available at the time given the national screening programme had just begun. It reports new data on FIT-based colorectal cancer screening which has not been reported elsewhere and is relevant to other national screening programmes, especially given the increasing move towards FIT as the frontline test in population based screening due to its improved sensitivity and practicality. Low uptake however is not just an issue for males; as overall uptake of FIT based screening seems suboptimal and the thesis reports not just on factor influencing male uptake, but also female uptake. The thesis provides the first review, to the best of our knowledge, on international uptake overall and by gender, using FIT-based screening. Subsequent studies within the thesis have provided new data on factors influencing uptake in FIT-based screening and has identified areas for further research aimed at improving uptake.

7.3 Implications of Findings

Wardle et el have argued that any health technology in which uptake is unequal across groups runs the risk of creating or widening health inequalities(15). This is indeed the issue for colorectal cancer screening in Ireland and elsewhere. FIT is a relatively new technology and in Ireland this is the first time an organised population-based screening programme has offered a screening test which can be carried out at home. Furthermore this is the first time the male population has been invited to take part in organised cancer screening. The studies conducted for this PhD project point to disparities in uptake by sex. Given the higher colorectal cancer incidence and mortality among males, not just in Ireland but worldwide (16), tackling low uptake of, and disparities in, public health initiatives such as colorectal cancer screening is of vital importance.

However it must be noted that we found consistently smaller differences in uptake by gender in comparison to the differences observed with deprivation. Gender based relative risk for non-participation among males were always significant (Chapter 3 converted RR 0.95; Chapter 4 RR 0.96; Chapter 6 converted RR 0.96) yet noticeably smaller than the deprivation gradients in uptake (very disadvantaged RR 1.06 compared to the affluent group RR1.26).

Initially, it was intended that the interviews and survey would have been nested within the national programme (and this was agreed with the programme) but delays in programme implementation meant this became impossible. Therefore the studies were done within the Tallaght programme instead. Although that programme took

part in a defined area, the studies may still be informative for the national programme. The findings of this thesis are now becoming manifest in data from the BowelScreen programme, which is just beginning to come into the public domain. (5) The recently published first report from the programme revealed that uptake is 40% (488,628 invited and 196,238 screened); this is considerably below the programme target (50-60%) and even below the international average reported in our systematic review and meta-analysis. Furthermore uptake in males in the national programme is far below that among females (36% vs 44% respectively). This also needs to be considered in the context of the detection rates of cancer within the programme; male detection rates were almost double that of female rates belying the increased risk of the disease among males (5) and the need to improve uptake among this group.

In Ireland male colorectal cancer has been positively associated with population density (14% higher in the most densely compared to the least densely populated areas) and unemployment (11% higher risk in the areas with the highest levels of unemployment compared to areas with the lowest levels) (17). The All-Ireland Cancer Atlas, which was based on cancer diagnosed between 1995 and 2007, has also shown that in areas with the highest proportions of those aged over 75 who live alone, the risk of colorectal cancer is 19% higher in females and 10% higher in males, compared to areas with the lowest proportion of persons over 75 who live alone(17). Analysis of data among our screening population (TTC-CRC-SP survey) indicates that overall 24% of our sample were not in cohabiting relationships, but among non-users this was higher at 30%, increasing in those aged 59 or less to 46% (compared to 20% among users of the same age) and 36% among those aged 70 and

over (compared to 29% among users). Our finding that the influence of a partner is associated with increased uptake in colorectal cancer screening raises a serious issue about those who live alone in Ireland and their participation in colorectal screening. This is a not a readily modifiable factor and little research has been carried out in the area(18).

A number of interventions have been tested aimed at increasing uptake of colorectal cancer screening, most often related to FOBT or endoscopic based tests. Strategies to improve uptake vary according to context (healthcare systems, and culture), type of test (faecal based or endoscopic tests) and target group (ethnicity, age, gender). In spite of this, evidence informing strategies to improve participation in low uptake groups is scarce and needs to be built upon (19). Interventions utilising client reminders and reduction of structural barriers in colorectal cancer screening have proven somewhat efficacious, although only for FOBT screening (20–22). While psychological variables are often associated with participation their utility as targets within interventions have proven less successful (22). Wardle et al have pointed out that more needs to be done to understand the social patterning of screening participation and to reduce social inequalities in screening (22), while Weller and Campbell have recommended strategies that incorporate male perspectives and attitudes towards preventative health services in order to overcome gender specific barriers to screening (19).

Our work has established a foundation of evidence on FIT-based colorectal cancer screening uptake. Although much is still to do, we have a starting point from which we can now begin to develop strategies and interventions aimed at improving

uptake. While it would seem from our findings that potential interventions should focus on negative attitudes and beliefs about cancer and screening there is still much data remaining to be analysed, including data relating to defensive information processing. Potential interventions could focus and psycho-educational interventions or media based campaigns to reduce negative attitudes and beliefs about bowel cancer screening. However we are cautious in making recommendations before our behaviour change analysis is conducted which will provide us with the opportunity to establish stronger evidence on interventions which will potentially increase uptake in the national screening programme. It should also be noted that any interventions will likely only improve uptake in small incremental increases.

The challenge now is the task of investigating how we can intervene in these negative beliefs and attitudes in order to improve uptake. The data collected in this thesis provides an opportunity to examine the behaviours of screening users and non-users in order to identify behaviours which may be modifiable and therefore amenable to the development of interventions to improve uptake. Domains which are likely to influence behaviour have been identified and can be targeted by relevant behaviour change theories (BCTs). Identification of BCTs can be informed by a published matrix which has mapped theoretical domains and behaviour change techniques using an expert consensus approach(23). All relevant techniques mapping onto the identified theoretical domains can be listed as potential intervention BCTs. This process can be performed separately for males and females in relation to the key target behaviours.

Active stakeholder engagement in this process would ensure that such research would address key questions and challenges being faced by stakeholders and would inform policy and practice. The process would require the engagement of key stakeholders in exploring findings and potential interventions in relation to how to operationalise these in order to improve uptake within a screening programme. How BCT's can be targeted through an intervention could be explored in terms of operationalising intervention functions within current screening programme structures and design. The use of the APEASE criteria could be applied to assess the likely; (i) Affordability; (ii) Practicability; (iii) Effectiveness and cost-effectiveness; (iv) Acceptability; (v) Side-effects/safety and; (vi) Equity of the selected intervention functions(24,25).

The potential to design interventions which will improve uptake in males and females, and indeed by deprivation, is now ripe for development given that we have a population that has only recently been exposed to national organised population based screening. Our findings indicate that fatalism is a key barrier to screening and will likely be a factor in any behaviour based intervention aiming to improve uptake. While no differences were observed in fatalistic beliefs about screening in males and females, there may well be differences in underlying factors through which fatalism operates in each gender, which we aim to explore in our future analysis of defensive information processing. Therefore it may well be a case that interventions (through messages in psycho-educational programmes or media campaigns) need to be tailored by gender or indeed at the varying levels of deprivation within communities. The planned next stage of this work will seek to establish how males and females differ in their attitudes to screening and will seek to understand the underlying

mechanism through which individuals, both at the level of gender and deprivation, avoid the opportunity to be screened for colorectal cancer.

The work undertaken within this thesis is both warranted and appropriate given the roll out of the National colorectal cancer screening programme, BowelScreen. It is all the more relevant now given the results of the first round of screening which took place while the work in this thesis was being carried out. The National Screening Service have reported that uptake in the first round is low (40%) and male uptake lower again. Given the higher rates of detection of cancers among males in the first round of national screening in Ireland our study has pre-empted the need for action in improving uptake of FIT based colorectal cancer screening in the population. At the outset of round two of national FIT based screening our study provides valuable evidence which the national screening programme can use to begin to tackle low uptake, thereby helping to achieve the goals of the programme, in short to reduce colorectal cancer incidence, morbidity and mortality from the disease in the population.

The National Screening Service should now begin to examine uptake by gender and how findings in this thesis, namely that beliefs about cancer and cancer screening, negatively influence participation decisions. Vital also is the need to explore the effect of deprivation on uptake nationally and if this moderates gender based uptake at the national level. The National Screening Service has already begun to place a focus on these findings and have taken note of the importance of this thesis to the successful roll out of the national BowelScreen programme. To this end BowelScreen has provided some funding to establish the next phase of this study to

establish an intervention prototype which aims to improve gender based uptake, described above.

7.4 Recommendations for future research

Chapter 2 identified issues related to increasing rectal cancer mortality in Ireland. We suggested that there is potential that this increase, which has not observed in most other European countries (26) may be a result of misclassification of colon and rectal cancer deaths particularly given the evidence that at least 30% of death certificates are likely to be incorrect and 20% of autopsies unexpected findings can only be diagnosed by histological examination (27). In addition the potential underuse of radiotherapy (particularly preoperative radiotherapy) and the underuse of multidisciplinary team meetings in the treatment of rectal cancer may also provide an explanation for the rise in mortality. Further investigation is required to explore the extent and nature of misclassifications on death certificates in European countries in recent years, comparing countries with rising and static rectal cancers. But examination of the underuse use of pre-operative radiotherapy and multi-disciplinary meetings require further investigation in considering the increase in the rates of rectal cancer mortality.

Given FIT is now recommended as the test of choice in population based screening programmes it would be useful to update the systematic review in chapter 3. It is likely that more relevant studies of population-based screening have been published. The systematic review also suggests further investigation into factors associated with participation in FIT based screening.

While the systematic review did not find any differences in uptake by sex according to the number of samples that are required for a successful test, other authors (28) have reported improved uptake through simplification of the sampling strategy (i.e. using two rather than three samples). The strategy used in our screening population used 2 samples, and within the national screening programme only one sample is required. Reported lower uptake in the national screening programme compared with the TTC-CRC-SP indicates that perhaps further investigation is required.

While the work discussed in this thesis has presented evidence on factors influencing uptake there is still a need to carry out further investigation. The thesis has identified significantly lower uptake in males but was unable to identify what drives these uptake differences, despite the identification of factors influencing uptake overall. Many other avenues exist in terms of the exploration of factors driving low uptake in males but these need to be allied with an exploration of uptake in females also. In chapter 4 and 6 we reported that male uptake was significantly lower than female uptake and that this was not attenuated by deprivation. However given our studies were carried out in a predominantly deprived setting we would suggest a re-examination of this within the National BowelScreen programme as more complete population level deprivation data on screening uptake will be available.

In both our qualitative and quantitative cross sectional studies we identified the impact of the influence of a partner on screening decisions, especially among males. Research examining different household invitation strategies within the national screening programme would be useful to determine their impact on uptake. The other side of this finding is the fact that those not in cohabiting relationships, or living alone are less likely to take part and these present an opportunity for research into what barriers exist for this particular group, notwithstanding the difficult of

reaching this group in research. We have also identified a small number of male participants in our qualitative study who resisted doing the FIT test due to an underlying fear of the potential outcome of screening (i.e. a diagnosis of cancer). Such issues require further investigation.

As discussed in the limitations section of this chapter and in chapter 5 and 6, there is a need to investigate further the effect of poor health literacy on colorectal cancer screening uptake in Ireland's population. We therefore suggest a broader investigation of health literacy in the population, one which takes into account a greater range of deprivation classes. This could be carried out within the BowelScreen programme upon invitation, but should also investigate potential differences in screening information comprehension and subsequent decisions to participate in screening.

As alluded to in the discussion of the findings of the qualitative study (Chapter 4) and the cross-sectional study (Chapter 6), the potential importance of the concept of defensive information processing and believe this should be a focus of future research aimed at investigating potential underlying differences in males and females processing of health information. Defensive information processing may underlie the findings on negative beliefs and emotional attitudes related to cancer and cancer screening and may be a potential avenue for explaining the mechanisms by which individuals justify non-use of important public health initiatives aimed at improving the health of the population. In addition, this may well provide evidence on the potential factors which underlie differences in male uptake. Investigating defensive information processing may provide an avenue through which we can understand how males and females deny the need to take part in FIT based

screening. This is one area of research that would be fruitful in the move towards the development of behaviour based interventions to increase uptake of FIT.

Given the low response rate of non-users and the potential that they are a selected group it would be useful to undertake an investigation of non-users in the population. This would provide greater insight into the characteristics of non-users and the potential reasons for non-use which might provide opportunities to target particular groups of non-users who may be more amenable to, or ready for, uptake interventions. In the UK the use of omnibus surveys have provided opportunities to gauge cervical cancer screening history and future intent to be screened, providing valuable data on screening non-users (29). Such research should be considered within the Irish context.

As discussed in the implication section above, future research on the development of interventions to improve uptake in males and females should be carried out to continue the progress made here on FIT-based colorectal cancer screening. This should involve the further analysis of the qualitative and quantitative data collected for this thesis and the review of interventions aimed at improving colorectal cancer screening uptake. Using relevant behaviour change techniques to identify interventions and engaging with stakeholders to ensure key questions and challenges are addressed would ensure the development and testing of a replicable intervention that illuminates the principles and processes underlying behaviour change within a colorectal cancer screening programme.

7.6 Conclusion

This thesis shows that significant disparities in exist in male uptake of FIT-based colorectal cancer screening. Furthermore uptake within FIT-based screening programmes is low in general which is a cause of concern in relation to the aim of population based screening to reduce incidence and mortality from the disease. Factors influencing people's non-use of FIT screening in the population include holding negative beliefs about cancer and negative emotional attitudes to the FIT-based screening test. FIT-based colorectal cancer screening is a relatively new technology and is now the screening test of choice and the marker against which new tests should be compared and assessed (30). The complexity of the problem of improving uptake should not deter us from seeking solutions through the development of interventions aimed at modifying non-users behaviour and attitudes to FIT-based screening. The aim of maximising screening uptake to maximise the reductions in incidence and mortality can only be achieved by tackling low uptake. This thesis has demonstrated the need for interventions aimed at improving uptake within FIT-based colorectal screening programmes.

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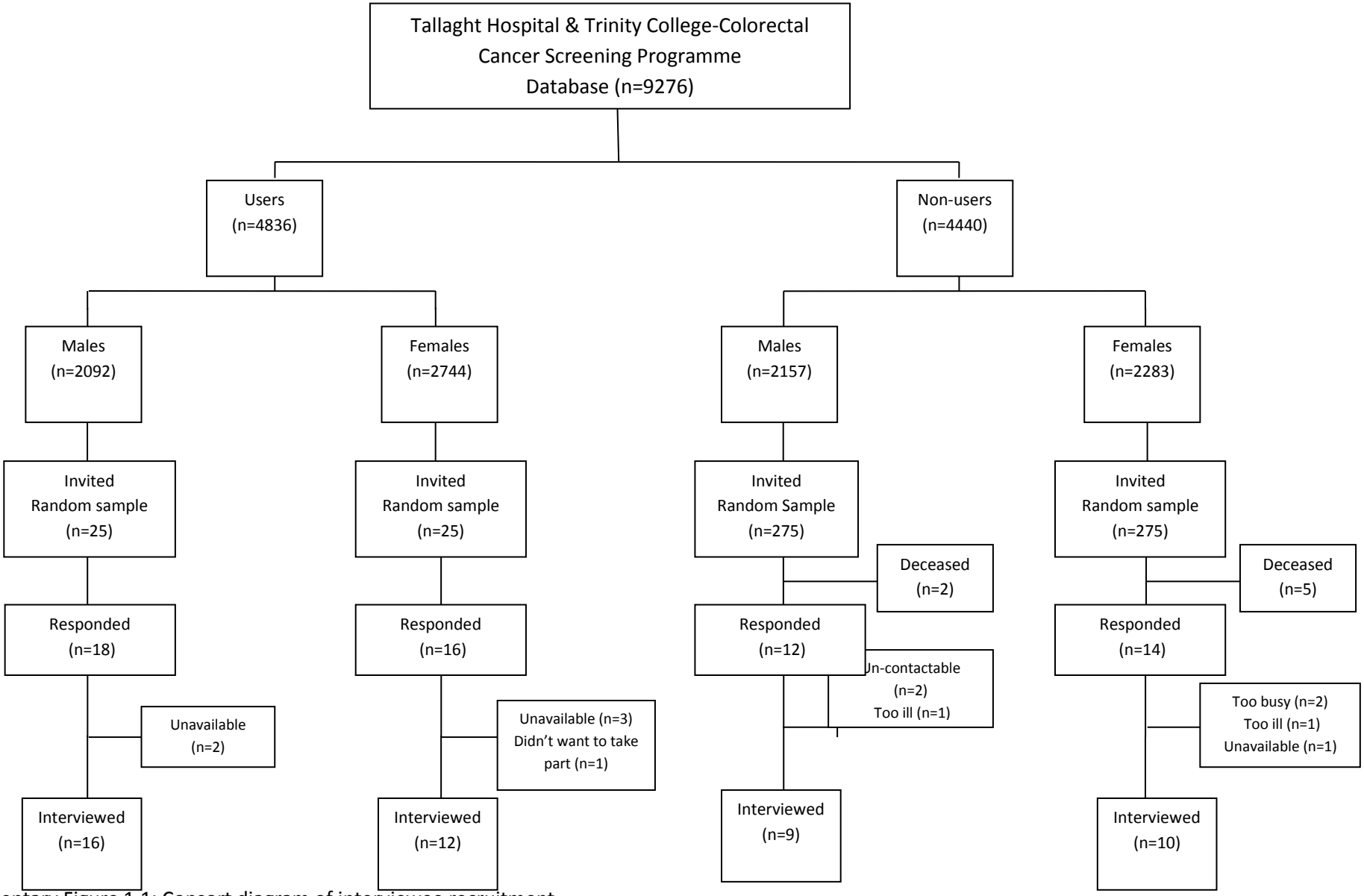
Appendix A: Supplementary material (chapter4)

Supplementary Table 1.1: Stratified Poisson regression by uptake in various rounds

Characteristic	Both rounds			Round 1 only			Round 2 only		
	RR	95%CI	p	RR	95%CI	p	RR	95%CI	p
Gender									
Female				-	-				
Male	0.87	0.83 - 0.90	0.000	0.81	0.71 - 0.92	0.001	0.92	0.82-1.03	0.142
Age									
0-59	-	-	-	-	-	-	-	-	-
60-64	1.16	1.09 - 1.23	0.000	0.84	0.71 - 0.99	0.040	0.96	0.83-1.12	0.637
65-69	1.30	1.22 - 1.38	0.000	0.94	0.79-1.13	0.537	1.14	0.98-1.34	0.086
70-74	1.20	1.11 - 1.29	0.000	1.02	0.83-1.25	0.874	1.11	0.92-1.33	0.282
75+	1.22	1.07 - 1.39	0.002	0.73	0.43-1.22	0.224	1.38	1.02-1.87	0.038
Deprivation									
Very disadvantaged	-	-	-	-	-	-	-	-	-
Disadvantaged	1.35	1.22 - 1.50	0.000	1.11	0.89-1.37	0.348	1.07	0.89-1.29	0.454
Marginally below average	1.80	1.64 - 1.98	0.000	1.43	1.16-1.76	0.001	1.28	1.07-1.53	0.006
Marginally above average	1.90	1.70 - 2.11	0.000	1.82	1.40-2.36	0.000	1.37	1.07-1.75	0.011
Affluent	2.34	2.04 - 2.67	0.000	3.32	2.28-4.83	0.000	2.69	1.92-3.78	0.000



Supplementary Figure 1.1: Consort diagram of interviewee recruitment

Appendix B: Supplementary Material (Chapter 5)

Tell me a bit about yourself	
Live here always?	All
Family	All
Occupation	All
General health/ other conditions	All
How often would you attend a GP/ when was the last time you attended /	All
Exercise/ diet	All
Health information and general understanding	All
What is your overall feeling about our health system? Trust?	All
First invitation:	
What were your first thoughts on receiving invitation?	All
Was this different on second invitation?	All
Aware of screening before? Any screening - CRC screening - local/ Nation	All
Taking test – did you want to?	All
Decisions	
Why did you decide to do the test?	All
Did you make an attempt to do the test?	Non-users
Why did you decide not to do the test?	Non-users
Others - did you speak or discuss the test with others?	All
Do you regret not doing the test - discuss	All
Test	
How was it – easy/ difficult?	All
Confident – in doing test correctly (self testing vs GP testing)	All
Comfortable - Time / sampling/ storage/ smell/ disgust/ information/ support/ assistance	Users / attempters
What would make test easier?	All
Were there other factors that made it difficult?	All
Results	
How long did it take to get your results?	
What was your result?	Users
What was it like waiting for the results?	
Did you understand the result?	Users
Were you confident result was correct?	
What impact did the result have on you?	Users
Screening - general	
Screened before? - Mammogram/ cervical/ breastcheck - PSA - CRC	All
How do you find those screening tests?	All
Importance of screening you've taken part in?	All
Importance of screening in general?	All
What do you feel the purpose of screening is in general?	
Bowel cancer	
Experiences of bowel cancer (BC)	All
Causes of BC	All
Treatment for BC - effective/ ineffective	All
Whos at risk of BC	All
Your risk of BC	All
Finally	
Men are less likely to be screened - why do you think this is?	All
Finally - Will you take part in the national screening programme, BowelScreen?	All
Is there anything you'd like to add which we haven't discussed?	All

Supplementary Table 2: Illustrative quotes for domains potentially influencing screening decisions in users, by gender

Domain	Female users	Male users
Environmental context and resources	My paternal grandmother had it [colorectal cancer], and she was very bad, she ended up with a colostomy bag, which I just think is the most hideous thing in the world, myself. And she died a bad death, shall we say, so that certainly sticks in my mind. (P-10)	But I had a brother died of colon cancer, so the family took a bit of an interest then. Because we have a niece in England who kind of pushes a little bit, like, "You need to get this done." So she got her dad, a brother of mine, to do it – he's sadly passed away since. So there's an interest there and an interest to follow up alright, yeah. (P-31)
	She had bowel cancer. Well, her bowel burst, actually, she's lucky to be alive. I thought, oh no, I need to get this done, because there's slight changes, do you know (P-9)	And certainly in light of the two guys, friends of mine who are in trouble now. So I would certainly be very conscious of it. (P-28)
	Yeah, because they give you instructions. But the instructions, you know, you have to poo on a piece of paper. It might just go down the loo. You are not going to be fishing it out. (P-1)	Easy to do, easy to do. Once you follow the… As I said, they explained the test really well. If you followed what they'd said, you'd no problem, no problem whatsoever. It was easy to understand. (P-27)
	I'd think it would probably be more effective if it was maybe on a disc or a dish rather than, do you know, like… you know the way the screening is done, is like a swab, a tiny, tiny swab, and I think… I know, talking to people - I didn't have a problem because I would be got back to presumably if it hadn't been successful (P-5)	That's not a problem, you have your own bathroom, you have your privacy, you do it all, seal it up, bring it down in a package. It's not a problem, it's so easy. (P-31)
Beliefs about capabilities	No problem, no problem. Like, well, you know, my attitude is if you have to do something you'll find a way to make it easy for yourself kind of, you know what I mean.(P-4)	Oh it's no problem, you just do it. I mean, maybe it's a bit embarrassing given the nature of what you are doing, but it's not really, because you do it privately..../Normally, doing anything like that I'd be conscientious enough about reading instructions. I don't like to do things just, like, willy-nilly, you know. (P-36)
	Well, I thought so. I mean, it's pretty simple to do, just take the little stick and… *[Laughter]* . It's not exactly rocket science. *[Laughter*]. (P-7)	Yeah. I did exactly what I was asked to do, yeah..../ It was easy enough, yeah. Yeah, you just prepare whatever you have to do upstairs and do it, yeah. (P-32)
Beliefs about consequences	But I always feel that if you had to get a cancer, it wouldn't be one of the worst *[colorectal cancer]* , because it is treatable, and if it's caught in time I think you have a better chance than you have if you got pancreatic cancer. I'd prefer to be told I had bowel cancer than pancreatic cancer. (P-3)	Well, I'd have thought it all depends on how advanced it is before it's caught. It seems to be… like, you hear people have cancer, and they say, 'Oh, they were just too far gone.' Like, I think the frightening thing about cancer is you have it for so long and that you don't know you have it, and then when they discover the cell, you know it's… But I would believe, if they got it in time, if they were screening, and all that, that's the way I believe in it. Well, it's like anything, I suppose, if you get it in time. (P-26)
	Well, if they are caught quickly… Like, if I hadn't, God forbid, had it then, I would have been quite… I would have… after getting over the shock, I would say, 'No, I'll be alright.' I'm convinced, if you can get it at the right time… I think the trouble is when it starts spreading, obviously, you know. So if you can prevent it, as I say, or…? (P-9)	What did come into my head, "At least if it comes out the wrong result for me, at least it's known about and it can be treated." So that was in there that, if I'm being invited to do this and I'm detected as positive, well then they will do something and they'll treat me. I won't have to go to my doctor and then go to a consultant. This is what I was thinking.(P-31)
Social Influences	I might actually even be listening to a topic, or reading a topic, or a discussion about bowel cancer, or if I came to a bowel cancer awareness week or breast cancer or bowel cancer or whatever, it would make me think, and it's "oh I must follow up on that and have all that checked out for myself", even though there is no bowel cancer or breast cancer in my family. (P-3)	Yeah, she said it [female spouse]. I thought she had looked to get it done, I didn't know anything about it the week beforehand. And she said, "No, just send it in the post, and they write the thing down." And I thought, why not? It's a free chance you get of a check-up. (P-38)
	That's the way it was. But I did put it to one side. And I kept on to my husband as well to do it, but he wouldn't do it. (P-6)	She nagged me into it [female spouse], so I did it. And when I got the results it was great. And I did the second one (P-35)
Emotions	I thought brilliant....Great idea. Any of those tests for prevention, I would say, is a great idea. (P-1)	I was absolutely delighted; I thought it was a wonderful idea. I was absolutely thrilled to take part in it, I have to say..../Oh I was just happy to see that they confirmed my own view of how I was, you know. Absolutely delighted. (P-34)
	Grand. It's something else I don't have to worry about. 'I passed that, so I don't actually have bowel cancer. Isn't that great?' (P-2)	Its great to have it checked because the the more people you've met or have known that have had cancer, and the closer you are to getting it, the more frightening it becomes, especially when people die, obviously. (P-29)
Knowledge	Well, I look at my family background and my grandparents and my parents and my siblings and all of that, and bowel cancer is not a thing I would be scared of, quite honestly. I wouldn't be. (P-3)	Well, I mean, there is a risk. I'd be very, very conscious of it. And even more so now. I'm probably due… I think it's about two years since I had the colonoscopy, and it's probably time to have another one. I would, certainly. I'd be conscious of it, very conscious of it. (P-28)
	Er, it's funny, I suppose it's one of the cancers I would think, no, you won't get that. Yeah, it's just maybe to do with diet and lifestyle, is a lot to do with it probably. (P-6)	Well, at the moment, after doing this *[colonoscopy]* I think I'm okay. (P-29)

Supplementary Table 3: Illustrative quotes for domains potentially influencing screening decisions in non-users, by gender

Environmental context and resources	I know a neighbour up there who did the bowel thing with her husband. Husband was alright. Went there and was alright. She came in and nearly lost her life, because they punctured her bowel. Priests know. Their family was all called. It was dreadful. That put the *[swear word]* up everybody in the estate (P-22)	Because it said to do it at the weekend [FIT test]and put it in the fridge. So I just kept putting it off. I mean, in and out of the courts for the last… I mean, I'm going to the High Court now. The kids were all taken out because she abused them. Mad stuff, crazy stuff, about 10 years ago. So I've been down the courts for the last 12 years. (P-45)
	I just didn't want to. Why didn't I do it? Yeah, because my eldest young fellow… I got it the morning after my young fellow nearly died the night before and I just – '*[Swear word]* – I'm sick of hospitals' – and it was all bowels – I just couldn't. (P-19)	Because I was separated, you see. I was in the house. I got a judicial separation. A lady judge told my wife she would have to sell the house and give half the proceeds to me, which wouldn't be an awful lot of money, but I had two daughters living in the house. So if she sold the house, it would do more damage.... I've gone through all that myself. And I decided… I didn't do anything about it. (P-40)
	You have to put it in the fridge. That's the only thing. But I suppose you can put it in an extra bag and leave it in the fridge. Well, I have another fridge now. *[Laughter]* But at the time I was saying, "Oh God!" But that's… I know it's stupid and all but… (P-17)	
	That's what put me off, the catching of it *[faeces]*. That would put me right off it. How would you catch it?//Or probably I'd just seen the size of the thing and panicked and thought, 'I'm not putting that into that *[container]*.' (P-13)	There's nothing I could do about it. It wasn't my fault. Probably wasn't their fault. It was GPOs *[swear word]* fault, or someone like the *[swear word]* bleeding postman that comes around. They skip [swear word] half the doors around here. (P-42)
	I think it's just by luck if you are able to get yourself back on the road. I don't honestly think they *[medical profession]* know what they're doing. I think so, anyway. (P-17)	I had to solve a problem with the mail in my house. ...// Every post I get is always opened. (P-40)
	The health system in general is crap, especially *[name]* Hospital. It's the worst hospital ever. // I've nothing against the nursing staff. The nursing staff at any hospital is brilliant, brilliant. It just depends on the doctors. (P-19)	
Beliefs about capabilities	Well, when I saw what you had to do, I couldn't cope with that *[faecal sampling]*. Yeah... I wouldn't find it very… well, pleasant is not the word but…You know. I suppose nothing medical is, is it?....Nothing medical is pleasant. (P-15)	Yeah, you put the sheet down the toilet pot when you go to the toilet, naturally, and you have some and you put back into the bowl and send it off. Yeah...I'd do it myself now. I've no problem doing it now. (P-39)
	I didn't. I tell you why. For hygiene reasons I didn't do it. I thought, 'Oh God, I'm not doing that.... I just thought, 'I'm not doing that. That's just too messy. I can't be dealing with that.' So I said, 'No... not happening. (P-13)	
	To me, you know your own body. And if I thought… I have a young one with Crohn's disease, so I know if there's something wrong with your bowel, I know exactly when to go. ....I just didn't want to...//My attitude is – I know it's probably wrong, but if it's not broken, don't fix it. (P-19)	
Beliefs about consequences	I don't know if it's one of the bad ones *[colorectal cancer]*. I mean, my father-in-law died from lung cancer and that was a bad one. I think bowel... I don't know. It'd probably be fairly invasive and end up with bags and all sorts of things. (P-18)	I'd say they'd be dead. Because there's no cure for cancer is there, not that I know of anyway. I mean, you get cancer, you're… eventually you're going to go, and that's the way of it, I think. There's very few people I know that have lived that had bowel – not that had bowel cancer but had cancer. They've all died. (P-47)
	I don't think it will be much... Bowel....I don't think they have a good chance really. (P-7)	Yeah. I don't believe there's any cure for it. I've often read, all down through the years, people getting cancer tend to get cured. But these people get it back after three or four years, then they kick the bucket. (P-42)
	I think they should… the bowel should be taken completely out and put on a bowel bag, because unless you get to the root of it, to take the whole broken part out, you'll never be right. But that's my opinion of it anyway. (P-19)	Yeah, I think there's a, kind of, subconscious… in my case - and I say subconscious deliberately, because I certainly wasn't conscious of it at the time - but I think, perhaps, there's this subconscious idea that if I partake in this I'm going to be putting myself in the firing line to some degree. Do you know what I mean? I'm going to get news that I don't particularly want to hear. I didn't consciously feel that. But I suspect that with men, that

Supplementary Table 3: continued…

Domain	Female non-users	Male non-users
Social Influences	She was extremely lucky [*neigbour who experienced a punctured bowel as a result of a colonoscopy*]. If she was here now, she'd sit there and she'd tell you the whole story, because I think she's told me this now about three times. She was saying, "If you don't feel you have to go, don't go. If you really feel that you've done this test and there's nothing, don't go in." (P-22) The mammogram one, she *[GP]* nagged me until I got that done, but she doesn't nag over that one *[FIT screening]*. Do you know what I mean? (P-13) Well, it was my mother, when I got the letter my mother said, "Throw that in the bin, you don't want to know anything about yourself." (P-16)	My eldest daughter, now, she said I should do it. "Do the test. It's not going to cost you anything. It's not going to do you any harm." She said, "If there's anything, at least you'll know". I said, "If there's anything there, do you not think I would know?" Because you think you know everything yourself, don't you? Which is wrong, we don't. (P-44) Now, saying that, my wife did it, okay, we both got it at the same time, the samples and stuff, the package. She did it first. And she said to me, "Did you do it?" "Aye," I said. But I didn't. (P-46)
Emotions	And I thought, 'I'm not doing that' *[faecal sampling]*. Yes... If it had been probably- oh God, it sounds disgusting. (P-13) I'm just fed up of hospitals. I go… Let's say I go if I have to. But given a choice… (P-20) Then I have a very hazy recollection of being asked about bowel screening. I don't know. I can't find out that something else is wrong with me. Right now I cannot deal with that. I was a bit of the ostrich, bury your head in the sand, pretend it's not happening. (P-21) But I think because of the word 'cancer' as well. I know no one wants it, but…//Yes, I have a big fear about cancer. (P-17)	As I said, the C word is a bogey word to everybody, you know what I mean? (P-39) At the time it was, yeah, it was a fear of dying. Now I wouldn't care, it wouldn't bother me now. (P-47) Yeah. But cancer's a dirty word, you know what I mean? If you're not… I don't mean that in a semi-joking way. It's a frightening word. A frightening word, because, as I've said, I've seen so much of it over the years. You know, it's, kind of, will I, won't I? (p-39) You know -regarding cancer, it's just a bad word. It's a bad word…..// I feel that the cancer, it's just a nasty word. Its a nasty word that you dont want to hear. (P-46)
Knowledge	Because, probably stupidly in my case, there's absolutely no history *[colorectal cancer]* in either my parents, grandparents, great grandparents. The other two that would be more of a risk to, i.e. the breast cancer or cervical cancer, I keep on top of that. So I'd say, hopefully, praise God, it's pretty low. (P-13) Yeah. For the fact that it doesn't run in the family. I put myself at low risk, because none of my family died of bowel cancer. I know a few of them died of cancer all right, but not bowel cancer, so I'd put myself kind of in the low category of bowel cancer now. (P-19) That would have been on my mind, opening that pack, and looking at it and thinking, 'Well, I don't have the symptoms that [sister] had. If I have, I'll go.' That was my attitude. 'If I have, and I see any signs of anything that's abnormal, I'll go.' So, if you don't have it there, what can they tell you? Do you know what I mean? …I'm not being cocky about myself with not being ill. If you're every day going to the toilet and you haven't got problems, and you've no pains, you must be okay for the moment. (P-22)	That, again, I couldn't tell you *[about colorectal cancer and risk]*. I haven't a clue, to be honest. Not a clue. (P-41) Well, I don't know. Because I haven't even read about it, to tell you the truth, so I don't know what really causes it in the first place. (P-44) Now, the envelope inside the envelope, well, it was a packet rather than an envelope, a cushioned sort of thing so that it couldn't be, you know, wouldn't leak or anything like that. But you wiped your bottom and you sent this piece of paper off to the.. wherever, the lab. But I didn't, I didn't do it." (P-40)

Supplementary Table 4: Characteristics of interviewees at time of interview

	Male users	Female users	Male non-users	Female non-users
All participants	16	12	9	10
Age				
Mean age	66	66	64	65
Age range	58-72	58-72	55-77	56-78
55-64	6	5	4	5
65+	10	7	5	5
Marital status				
Married	12	8	5	5
Single/ Divorced/ Separated/ Widowed	4	4	4	5
Health care access *				
Private Health Insurance - Yes	10	6	-	2
Private Health Insurance - No	6	6	9	8
Medical card** - Yes	3	4	8	5
Medical card - No	3	2	1	3
Employment status (n)				
Working	5	4	1	2
Retired	11	8	3	6
Not working due to injury or illness	-	-	5	2

*Participants may be in multiple categories, i.e. hold a medical card and private health insurance
**A medical card is provided to citizens who are on reduced means and entitles the holder to free health care under the public health system including primary care.

Supplementary Table 5: Definitions of TDF domains which emerged as potentially influencing screening decision making

Domain	Definition
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, and adaptive behaviour
Beliefs about capabilities	Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use
Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of a behavior in a given situation
Social influences	Those interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviours.
Emotion	A complex reaction pattern, involving experiential, behavioural, and physiological elements, by which the individual attempts to deal with a personally significant matter or event
Knowledge	An awareness of the existence of something

Appendix C: Supplementary material (chapter 6)

Supplementary Table 3.1: Participant characteristics by gender and use or non-use of screening

	All					Male					Female				
	User		Non-User			User		Non-User			User		Non-User		
	n	%	n	%	*P*	n	%	n	%	*P*	n	%	n	%	*P*
Sex															
Male	1,014	51.0	184	59.2		-	-	-	-		-	-	-	-	
Female	974	49.0	127	40.8	0.007	-	-	-	-		-	-	-	-	-
Total	1988	100	311	100											
Age															
64 or less	950	48.7	183	59.6		463	46.49	97	53.3		487	50.94	86	68.8	
65+	1,002	51.3	124	40.4	*0.000*	533	53.51	85	46.7	0.910	469	49.06	39	31.2	*0.000*
Total	1952	100	307	100		996	100	182	100		956	100	125	100	
Deprivation															
Very disadvantaged	161	8.1	45	14.5		82	8.1	25	13.6		79	8.1	20	15.8	
Disadvantaged	524	26.4	116	37.3		257	25.4	57	31.0		267	27.4	59	46.5	
Marginally below average	1,034	52.0	122	39.2	*0.000*	532	52.5	84	45.7	*0.022*	502	51.5	38	29.9	*0.000*
Marginally above average	218	11.0	23	7.4		113	11.1	16	8.7		105	10.8	7	5.5	
Affluent	51	2.6	5	1.6		30	3.0	2	1.1		21	2.2	3	2.4	
Total	1988	100	311	100		1014	100	184	100		974	100	127	100	
Health literacy															
Adequate	1,641	84.7	242	80.4		819	82.8	145	81.0		822	86.6	97	79.5	
Inadequate	297	15.3	59	19.6	0.059	170	17.2	34	19.0	0.558	127	13.4	25	20.5	*0.034*
Total	1938	100	301	100		989	100	179	100		949	100	122	100	
Knowledge of others with CRC															
No	1,307	67.7	192	63.8		666	67.3	116	65.5		641	68.1	76	61.3	
Yes	624	32.3	109	36.2	0.180	324	32.7	61	34.5	0.651	300	31.9	48	38.7	0.128
Total	1931	100	301	100		990	100	177	100		941	100	124	100	
Knowledge of others with cancer															
No	374	19.3	63	20.7		186	18.8	32	17.7		188	19.9	31	25.2	
Yes	1,564	80.7	241	79.3	0.560	805	81.2	149	82.3	0.729	759	80.2	92	74.8	0.166
Total	1938	100	304	100		991	100	181	100		947	100	123	100	
Fear - Cognitive: Greatest health fear															
Strongly agree/ agree	1,167	61.8	189	64.7		582	60.3	109	62.6		585	63.4	80	67.8	
Uncertain	420	22.2	63	21.6		220	22.8	39	22.4		200	21.7	24	20.3	
Disagree/ strongly disagree	302	16.0	40	13.7	0.536	164	17.0	26	14.9	0.773	138	15.0	14	11.9	0.580
Total	1889	100	292	100		966	100	174	100		923	100	118	100	
Fear - Affective: Worry about cancer															
Strongly agree/ agree	758	40.2	127	43.8		340	35.3	73	41.7		418	45.4	54	47.0	
Uncertain	401	21.3	52	17.9		216	22.4	34	19.4		185	20.1	18	15.7	
Disagree/ strongly disagree	725	38.5	111	38.3	0.343	408	42.3	68	38.9	0.257	317	34.5	43	37.4	0.512
Total	1884	100	290	100		964	100	175	100		920	100	115	100	
Fear - Psychobiologic: Discomfort thinking about cancer															
Strongly agree/ agree	989	52.4	172	58.9		472	48.9	102	58.6		517	56.1	70	59.3	
Uncertain	387	20.5	55	18.8		212	22.0	35	20.1		175	19.0	20	17.0	
Disagree/ strongly disagree	511	27.1	65	22.3	0.102	281	29.1	37	21.3	*0.044*	230	25.0	28	23.7	0.783
Total	1887	100	292	100		965	100	174	100		922	100	118	100	

Supplementary Table 3.1: continued….

	All					Male					Female				
	User		Non-User			User		Non-User			User		Non-User		
	n	%	n	%	*P*	n	%	n	%	*P*	n	%	n	%	*P*
Positive belief: Continue with normal activity															
Agree	1,775	94.0	258	88.1		919	94.8	152	86.9		856	93.1	106	89.8	
Disagree	113	6.0	35	12.0	*<0.001*	50	5.2	23	13.1	*0.000*	63	6.9	12	10.2	0.191
Total	1888	100	293	100		969	100	175	100		919	100	118	100	
Positive belief: Cancer can often be cured															
Agree	1,757	95.4	255	90.4		901	95.1	149	89.2		856	95.6	106	92.2	
Disagree	85	4.6	27	9.6	*0.001*	46	4.9	18	10.8	*0.002*	39	4.4	9	7.8	0.100
Total	1842	100	282	100		947	100	167	100		895	100	115	100	
Positive belief: Going to doctor as quickly as possible increases survival chance															
Agree	1,822	96.1	281	96.2		930	95.9	167	96.0		892	96.3	114	96.6	
Disagree	74	3.9	11	3.8	0.911	40	4.1	7	4.0	0.951	34	3.7	4	3.4	0.878
Total	1896	100	292	100		970	100	174	100		926	100	118	100	
Negative belief: Treatment worse than the cancer															
Agree	960	52.2	168	59.6		404	42.7	87	51.8		556	62.2	81	71.1	
Disagree	881	47.9	114	40.4	*0.020*	543	57.3	81	48.2	*0.028*	338	37.8	33	29.0	0.065
Total	1841	100	282	100		947	100	168	100		894	100	114	100	
Negative belief: Would not want to know I have cancer															
Agree	196	10.5	48	16.7		95	9.9	32	18.6		101	11.1	16	13.9	
Disagree	1,674	89.5	239	83.3	*0.002*	867	90.1	140	81.4	*0.001*	807	88.9	99	86.1	0.376
Total	1870	100	287	100		962	100	172	100		908	100	115	100	
Negative belief: Cancer diagnosis is death sentence															
Agree	378	20.0	82	28.1		184	19.0	54	30.9		194	20.9	28	23.9	
Disagree	1,516	80.0	210	71.9	*0.002*	783	81.0	121	69.1	*0.000*	733	79.1	89	76.1	0.454
Total	1894	100	292	100		967	100	175	100		927	100	117	100	
Relationship status															
Co-habiting	1,508	76.4	212	70.0		853	84.7	139	77.2		655	67.8	73	59.4	
Not in cohabiting relationship	465	23.6	91	30.0	*0.015*	154	15.3	41	22.8	*0.013*	311	32.2	50	40.7	0.061
Total	1973	100	303	100		1007	100	180	100		966	100	123	100	
Social Support															
Poor	193	9.9	35	11.6		94	9.4	20	11.2		99	10.4	15	12.2	
Moderate	828	42.5	129	42.7		404	40.4	79	44.1		424	44.6	50	40.7	
Strong	928	47.6	138	45.7	0.625	501	50.2	80	44.7	0.385	427	45.0	58	47.2	0.660
Total	1949	100	302	100		999	100	179	100		950	100	123	100	

Table 3.2: Survey scale means

	No. of items	Score range	Overall mean ± SD	Male mean ± SD	Female mean ± SD
Cancer Fatalism inventory					
Users	15	0-15	2.90 ± 3.07	2.8 ± 3.04	3.01 ± 3.10
Non-users			4.15 ± 3.81	4.13 ± 3.80	4.17 ± 3.84
P			<0.001	<0.001	0.003
Emotional attitudes to screening scale					
Users	5	5-20	8.50 ± 3.04	8.40 ± 2.99	8.61 ± 3.08
Non-users			10.53 ± 3.38	10.46 ± 3.30	10.62 ± 3.52
P					
Social influence of partner					
Users	2	1-4	2.16 ± 1.11	2.47 ± 0.91	1.81 ± 1.20
Non-users			1.88 ± 1.07	2.17 ± 0.91	1.45 ± 1.15
P			<0.001	<0.001	0.001

Cross sectional survey instrument

A survey of participation in bowel cancer screening in men and women in Tallaght

tagg
Trinity Academic Gastroenterology Group

Irish Cancer Society
Research

Reference number: 212

The Adelaide and Meath Hospital/ Trinity College Bowel Cancer Screening Programme: new research study

Consent Form

Please circle Yes or No on each line below to show whether or not you consent (agree) to the various parts of the study.

I have received and read the information sheet. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	Yes / No
I agree: ▪ to take part in the project "BowelFIT - FIT uptake in CRC screening", by completing a questionnaire and returning it to the study team.	Yes / No
I understand that: ▪ my participation is entirely voluntary, and I am free to leave the study at any time, without giving a reason. This will not affect my medical care in any way. ▪ all information pertaining to me, or my family, will be protected by the principles of confidentiality and both national and EU Data Protection Legislation. ▪ no one will be able to identify me in any reports/papers published from the study. ▪ the study team will store my interview transcript permanently and confidentially (i.e. separately from my name and address) ▪ my personal identification details will be destroyed two years after completion of the study	Yes / No
I give permission for study staff to: ▪ anonymously share some of my data with collaborators from national and international research institutions, for further research into bowel cancer, and bowel cancer screening.	Yes / No Yes / No
I would like: ▪ a copy of a summary of the final report	Yes / No

_____	_____	_____
Name of participant (block caps)	*Signature*	*Date*
_____	_____	_____
Name of researcher (block caps)	*Signature*	*Date*

About the survey

We want to find out why people take part in, or decide not to take part in bowel cancer screening when a test is sent to their home. There are a number of different names for bowel cancer. These include:

Colorectal cancer

Colon cancer, and

Rectal cancer

We have sent this survey to you because – a few years ago - you were sent a bowel cancer screening test by Tallaght Hospital. ***Please complete the survey even if you did not do the screening test***.

If you complete and return the survey you will be entered into a draw for a €500 shopping voucher.

Completing the survey

Taking part in the study is voluntary. The survey will take about 30 minutes to complete. Please try to answer all of the questions that apply to you. There are no right or wrong answers, so please just tell us what you think.

Confidentiality

Please be assured that all the information you provide will be kept in the strictest confidence.

Questions

- For more information about the study, please telephone free phone no. 1800 283 097. If we are unable to answer, please leave a message and we will call you back.
- For someone to talk to, please call the Irish Cancer Society's National Cancer Helpline on FREEPHONE 1800 200 700.
- If you have questions about bowel cancer screening please contact BowelScreen on FREEPHONE 1800 45 45 55.

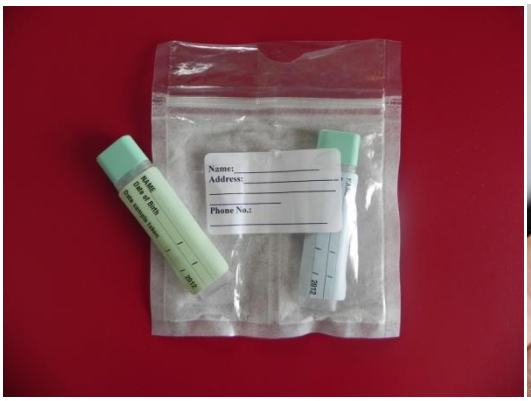
When you are ready to begin the survey, please turn the page.

Section A: A reminder of the bowel cancer screening test

In this section we are interested in finding out if people remember being invited by Tallaght Hospital to take part in bowel cancer screening.

Please answer all of the questions in this section by putting a '✓' in the boxes that apply to you.

During 2008- 2012 you were invited by Tallaght Hospital to take part in bowel cancer screening every two years using a new home based screening test called a FIT (faecal immunochemical test). The invitation and test kit was sent to your home by post. The test involved you going to the toilet and taking a small sample of your stool using a sampling device and placing it in a small plastic vial. You were required to store this in your refrigerator overnight, take another sample from another stool the following day and post both samples to a laboratory. Your results were posted to you and if you received a positive result you were asked to go to the hospital for a colonoscopy. If you received a negative result you were recalled for a second screening test two years later. An image of the FIT test is below.



A1. Do you remember receiving a screening test kit? Please tick one box only

- **Yes** ☐
- **No** ☐

A2. Did you return a screening test? Please tick one box only

- **Yes, I returned a screening test kit twice** ☐
- **Yes, I returned a screening test only once between 2008-2010** ☐
- **Yes, I returned a screening test only once between 2010-2012** ☐
- **No, I never returned a screening test** ☐

Section B: About you

In this section we want to find out something about the people who are completing this survey.

Please answer all of the questions in this section by putting a '✓' in the boxes that apply to you or by writing in the spaces provided.

B1. What year were you born? Year ☐

B2. What is your gender? Please tick one box only

- ☐ Male
- ☐ Female

B3. What is the highest level of education you have completed? Please tick one box only

- ☐ Primary school
- ☐ Secondary school
- ☐ Third level (e.g. college or university)
- ☐ Post-graduate (e.g. Diploma, Masters, Doctorate)

B4. What is your current marital status? Please tick one box only

- ☐ Married / living with partner / civil partnership
- ☐ Single / never married
- ☐ Married-Separated
- ☐ Divorced
- ☐ Widowed

B5. What is your current work status? Please tick one box only

- ☐ Working for an employer
- ☐ Self-employed
- ☐ Unemployed
- ☐ Looking after family / home
- ☐ Unable to work due to cancer, another illness or injury
- ☐ Retired
- ☐ Student

Other, please tell us:_____

B6. Did you have a medical card during 2008-2012?
Please tick one box only

Yes, all of the time ☐ Yes, part of the time ☐ No ☐

B7. Did you have private health insurance during 2008-2012?
Please tick one box only

Yes, all of the time ☐ Yes, part of the time ☐ No ☐

B8. How many people are so close to you that you can count on them if you have serious problems?

None ☐ 1 or 2 ☐ 3-5 ☐ 6 or more ☐

B9. In general, how much concern do people show in what you are doing in your life in general?

A lot of concern & interest ☐ Some concern & interest ☐ Uncertain ☐ Little concern & interest ☐ No concern & interest ☐

B10. How easy can you get practical help from neighbours if you should need it?

Very easy ☐ Easy ☐ Possible ☐ Difficult ☐ Very difficult ☐

B11. Have you, or any friends or family members that are close to you, ever been diagnosed with bowel cancer (this may also have been called colorectal, colon or rectal cancer)?
Please tick one box only

Bowel cancer	
Yes, me	☐
Yes, someone close to me	☐
Yes, both me and someone close to me	☐
Yes, but would prefer not to say whom	☐
No	☐

B12. Have you, or any friends or family members that are close to you, ever been diagnosed any other cancer?
Please tick one box only

Other cancers	
Yes, me	☐
Yes, someone close to me	☐
Yes both me and someone close to me	☐
Yes, but would prefer not to say	☐
No	☐

B13. Below are some statements about how people may feel about life in general. Please tell us how much you agree or disagree with each statement.
Please tick one box only on each line

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
In uncertain times I usually expect the best	☐	☐	☐	☐	☐
If something can go wrong for me, it will	☐	☐	☐	☐	☐
I'm always optimistic about the future	☐	☐	☐	☐	☐
I hardly ever expect things to go my way	☐	☐	☐	☐	☐
I rarely count on good things happening to me	☐	☐	☐	☐	☐
Overall, I expect more good things to happen to me than bad	☐	☐	☐	☐	☐

Section C: You, your health and the health system

In this section we are interested in finding out about your overall health and your feelings about the health system.

Please answer all of the questions in this section by putting a '✓' in the boxes that apply to you.

C1. In general, ***during the years 2008-2012*** would you say your health was...?
Please tick one box only

Very good ☐ Good ☐ Fair ☐ Bad ☐ Very bad ☐

C2. In your lifetime have you ever smoked more than 100 cigarettes?

Yes ☐ No ☐

If YES, do you smoke now?

Yes ☐ No ☐

If NO, in what year did you give up?

Year _____

C3. What is your weight without clothes?

_____ stones _____ pounds (or _____ kilos)

C4. What is your height without shoes?

_____feet _____inches (or _____cm)

C5. In a typical week in the summer and the winter how much activity do you do?
Write in the number of hours per week; insert 0 if less than 1 hour.

	Summer	***Winter***
Vigorous activity **(e.g. running, fast swimming, fast cycling)**	☐☐ Hours in a week	☐☐ Hours in a week
Moderate activity **(e.g. brisk walking, heavy housework, heavy gardening, gym, ordinary swimming or cycling)**	☐☐ Hours in a week	☐☐ Hours in a week
Light activity **(e.g. walking, general housework, cooking, shopping, gardening)**	☐☐ Hours in a week	☐☐ Hours in a week

C6. During ***2008-2012*** did you have any of the following conditions?

	Yes	No
Angina/ coronary artery disease	☐	☐
Asthma	☐	☐
Back pain or other chronic back condition	☐	☐
Bronchitis, chronic/ Chronic obstructive pulmonary disease (COPD)	☐	☐
Cancer	☐	☐
Cholesterol, elevated (high)	☐	☐
Colon problems (e.g. diverticulitis, irritable bowel, Crohn's disease)	☐	☐
Congestive heart failure	☐	☐
Diabetes	☐	☐
Hearing loss	☐	☐
Hypertension (high blood pressure)	☐	☐
Kidney disease	☐	☐
Nerve condition (e.g. Parkinson's disease, multiple sclerosis)	☐	☐
Osteoarthritis (degeneration of joint cartilage and the underlying bone)	☐	☐
Osteoporosis	☐	☐
Poor circulation (e.g. peripheral vascular disease)	☐	☐
Rheumatic disease (e.g. rheumatic disease such as fibromyalgia or lupus)	☐	☐
Rheumatoid arthritis (inflammation in the joints)	☐	☐
Stomach problem (e.g. gastritis, peptic disease)	☐	☐
Stroke	☐	☐
Thyroid disorder	☐	☐
Vision disorder (excluding wearing glasses)	☐	☐
Other, specify:		

C7. The following questions are about how much you trust your GP and hospital doctors. Please read each statement and tell us how strongly you agree or disagree with them.

Please tick one box only on each line

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Sometimes my GP cares more about what is convenient for him/her than about my medical needs	☐	☐	☐	☐	☐
My GP is extremely thorough and careful	☐	☐	☐	☐	☐
I completely trust my GP's decisions about which medical treatments are best for me	☐	☐	☐	☐	☐
My GP is totally honest in telling me about all of the different treatment options available for me	☐	☐	☐	☐	☐
All in all, I have complete trust in my GP	☐	☐	☐	☐	☐
Sometimes hospital doctors care more about what is convenient for them than about my medical needs	☐	☐	☐	☐	☐
Hospital doctors are extremely thorough and careful	☐	☐	☐	☐	☐
I completely trust hospital doctors' decisions about which medical treatments are best for me	☐	☐	☐	☐	☐
Hospital doctors would never mislead me about anything	☐	☐	☐	☐	☐
All in all, I trust hospital doctors completely	☐	☐	☐	☐	☐

C8. The Health Service Executive or the HSE is responsible for carrying out health service policy and managing and administering the health service in Ireland. Please tell us how much trust you have in the HSE?

Very high trust ☐ Rather high trust ☐ Not high ☐ No trust at all ☐ No opinion ☐

C9. How confident are you filling out medical forms by yourself?
Please tick one box only

Extremely ☐ Quite a bit ☐ Somewhat ☐ A little bit ☐ Not at all ☐

Section D: Attitude to screening

In this section we want to find out about your attitudes to bowel cancer screening.

Please answer all of the questions in this section, *even if you did not do the test*, by putting a '✓' in the boxes that apply to you.

D1. Please ***think back*** to when the bowel cancer test kit was sent to you in the post (i.e. **during 2008-2012**) and tell us how strongly you agree or disagree with each of the following statements. Please tick one box only on each line

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
When I received the bowel cancer test, I felt able to complete it	☐	☐	☐	☐	☐
Completing the bowel cancer test made sense to me	☐	☐	☐	☐	☐
I felt the bowel cancer test was a practical test to do when I received it	☐	☐	☐	☐	☐
If I got an abnormal result on my bowel cancer test I would accept an invitation for additional testing	☐	☐	☐	☐	☐

D3. Please ***think back*** to when the bowel cancer test kit was sent to you in the post (i.e. **during 2008-2012**) and tell us how strongly you agree or disagree with each of the following statements. Please tick one box only on each line

	Strongly agree	Mildly agree	Don't know	Mildly disagree	Strongly disagree
I wanted to do what my partner thought I should do about bowel cancer screening	☐	☐	☐	☐	☐
My partner thought I should have bowel cancer screening	☐	☐	☐	☐	☐
My doctor thought I should have bowel cancer screening	☐	☐	☐	☐	☐
I wanted to do what my doctor thought I should do about bowel cancer screening	☐	☐	☐	☐	☐

D2. Please ***think back*** to when the bowel cancer test kit was sent to you in the post ***(during 2008-2012)*** and tell us how strongly you agree or disagree with each of the following statements.
Please tick one box only on each line

	Strongly agree	Agree	Disagree	Strongly Disagree
I did not want to keep small amounts of stool in my house	☐	☐	☐	☐
I would not have had the privacy to do the test	☐	☐	☐	☐
I would only have done the test if I had symptoms of bowel cancer	☐	☐	☐	☐
It would have been unlikely that I had the time to do the test	☐	☐	☐	☐
Doing the test was disgusting	☐	☐	☐	☐
Doing the test was tempting fate	☐	☐	☐	☐
I would have been embarrassed if others knew I had done the test	☐	☐	☐	☐
Doing the test made me worry more about bowel cancer	☐	☐	☐	☐
I was afraid of getting an abnormal result from my test	☐	☐	☐	☐

Section E: Beliefs about cancer

In this section we want to find out about what people believe about cancer.

Please answer all of the questions in this section, *even if you did not do the test*, by putting a '✓' in the boxes that apply to you.

E1. Please ***think back*** to when the bowel cancer test kit was sent to you in the post (i.e. **during 2008-2012**) and tell us how strongly you agree or disagree with each of the following statements.
Please tick one box only on each line

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
I avoided information about cancer from the TV, newspapers and radio	☐	☐	☐	☐	☐
I avoided talking to other people about cancer	☐	☐	☐	☐	☐
I did not want any more information about cancer	☐	☐	☐	☐	☐
I didn't see the point of going to a doctor unless I was really sick	☐	☐	☐	☐	☐
I didn't go to a doctor unless it was really serious	☐	☐	☐	☐	☐
If I felt healthy, I did not go to the doctor for a routine check-up	☐	☐	☐	☐	☐
When I was sick, I tried to cure myself rather than go to the doctor	☐	☐	☐	☐	☐
I relied more on home remedies than on doctors	☐	☐	☐	☐	☐
I tended to avoid thoughts of bowel cancer	☐	☐	☐	☐	☐
I liked to ignore the idea that I could get cancer	☐	☐	☐	☐	☐
I hadn't faced the idea that I could get colon polyps	☐	☐	☐	☐	☐
I *did not* need to be screened for bowel cancer because I had regular bowel movements	☐	☐	☐	☐	☐
I *did not* need to be screened for bowel cancer because I included enough vegetables in my diet	☐	☐	☐	☐	☐
I *did not* need to be screened for bowel cancer because I didn't eat too much red meat	☐	☐	☐	☐	☐
I *did not* need to be screened for bowel cancer because I took good care of myself	☐	☐	☐	☐	☐
I *did not* need to be screened for bowel cancer because I exercised regularly	☐	☐	☐	☐	☐

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
I wanted to wait to get tested for bowel cancer until my other health concerns were under control	☐	☐	☐	☐	☐
I wanted to wait to get tested for bowel cancer until a time when I was not as busy	☐	☐	☐	☐	☐
I would have eventually got tested for bowel cancer, but had other health priorities at the time	☐	☐	☐	☐	☐
I wanted to get screened for bowel cancer, but I was waiting for a better test	☐	☐	☐	☐	☐
It's just not true that everyone 50 and older needs to be screened for bowel cancer	☐	☐	☐	☐	☐
Bowel cancer screening could not be all that important because few people I know had done it	☐	☐	☐	☐	☐
Bowel cancer screening couldn't be that important because my doctor had never told me I had to do it	☐	☐	☐	☐	☐
The medical evidence that bowel cancer screening is needed for everyone over 50 is not convincing	☐	☐	☐	☐	☐
There is not enough evidence yet to support the use of bowel cancer screening by all adults aged 50 years and older	☐	☐	☐	☐	☐
Few people get bowel cancer	☐	☐	☐	☐	☐
The claims that bowel cancer screening can prevent cancer are exaggerated	☐	☐	☐	☐	☐
The recommendation that bowel cancer screening must be repeated regularly for everyone over 50 years is overstated	☐	☐	☐	☐	☐
I couldn't do EVERYTHING that you're supposed to do for your health; it would be a full-time job	☐	☐	☐	☐	☐
Science always corrects itself; what is good today is bad tomorrow	☐	☐	☐	☐	☐
If you avoided all the things they say are bad for your health, you couldn't do anything	☐	☐	☐	☐	☐

E2. Below are some statements which are sometimes made about cancer. For each statement please tell us if you agree or disagree with each.

Please tick one box only on each line

	Agree	Disagree
I think if someone is meant to have bowel cancer, it doesn't matter what kinds of food they eat, they will get bowel cancer anyway	☐	☐
I think if someone has bowel cancer, it is already too late to get treated for it	☐	☐
I think someone can eat fatty foods all their life, and if they are not meant to get bowel cancer, they won't get it	☐	☐
I think if someone is meant to get bowel cancer, they will get it no matter what they do	☐	☐
I think if someone gets bowel cancer, it was meant to be	☐	☐
I think if someone gets bowel cancer, their time to die is soon	☐	☐
I think if someone gets bowel cancer, that's the way they were meant to die	☐	☐
I think getting checked for bowel cancer makes people scared that they may really have bowel cancer	☐	☐
I think if someone is meant to have bowel cancer, they will have bowel cancer	☐	☐
I think some people don't want to know if they have bowel cancer because they don't want to know they may be dying from it	☐	☐
I think if someone gets bowel cancer, it doesn't matter whether they find it early or late, they will still die from it	☐	☐
I think if someone has bowel cancer and gets treatment for it, they will probably still die from the bowel cancer	☐	☐
I think if someone was meant to have bowel cancer, it doesn't matter what doctors and nurses tell them to do, they will get bowel cancer anyway	☐	☐
I think if someone is meant to have bowel cancer, it doesn't matter if they eat healthy foods, they will still get bowel cancer	☐	☐
I think bowel cancer will kill you no matter when it is found and how it is treated	☐	☐

E3. Below are some statements which are sometimes made about cancer. For each statement please tell us how strongly you agree or disagree with each.
Please tick one box only on each line

	Strongly agree	Agree	Disagree	Strongly disagree
These days, many people with cancer can expect to continue with normal activities and responsibilities	☐	☐	☐	☐
Most cancer treatment is worse than the cancer itself	☐	☐	☐	☐
I would NOT want to know if I have cancer	☐	☐	☐	☐
Cancer can often be cured	☐	☐	☐	☐
Going to the doctor as quickly as possible after noticing a symptom of cancer could increase the chances of surviving	☐	☐	☐	☐
Some people think that a diagnosis of cancer is a death sentence. To what extent do you agree or disagree that a diagnosis of cancer is a death sentence	☐	☐	☐	☐

E4. Here are some more statements which are sometimes made about cancer. Please tell us how strongly you agree or disagree with each.
Please tick one box only on each line

	Strongly agree	Agree	Uncertain	Disagree	Strongly disagree
Of all the diseases there are, I am most afraid of cancer	☐	☐	☐	☐	☐
I worry a lot about cancer	☐	☐	☐	☐	☐
It makes me uncomfortable to think about cancer	☐	☐	☐	☐	☐

E5. Which, if any, of the following events happened to you ***during the period 2008-2012***?

Please tick yes or no for each event.

Event	Yes	No	Event	Yes	No
Death of a spouse/ partner	☐	☐	Son or daughter leaving home	☐	☐
Divorce	☐	☐	Trouble with in-laws	☐	☐
Marital separation	☐	☐	Outstanding personal achievement	☐	☐
Prison term	☐	☐	Spouse begins or stops work	☐	☐
Death of a close family member	☐	☐	Begin or end school or college	☐	☐
Personal injury or illness	☐	☐	Change in living conditions	☐	☐
Marriage	☐	☐	Revision of personal habits	☐	☐
Let go or fired at work	☐	☐	Trouble with boss	☐	☐
Marital reconciliation	☐	☐	Change in work hours or conditions	☐	☐
Retirement	☐	☐	Change in residence	☐	☐
Change in health of family member	☐	☐	Change in schools	☐	☐
Pregnancy	☐	☐	Change in recreation	☐	☐
Sex difficulties	☐	☐	Change in church activities	☐	☐
Gain of new family member	☐	☐	Change in social activities	☐	☐
Business readjustment	☐	☐	Took out a moderate loan or mortgage	☐	☐
Change in financial state	☐	☐	Change in sleeping habits	☐	☐
Death of a close friend	☐	☐	Change in number of family get-togethers	☐	☐
Change to a different line of work	☐	☐	Change in eating habits	☐	☐
Change in number of arguments with partner	☐	☐	Change in responsibilities at work	☐	☐
Took out a large mortgage or loan	☐	☐	Foreclosure on mortgage or loan	☐	☐

Please go to the next column

Section F: Future intentions

The Tallaght Bowel Cancer Screening Programme has now finished. There is a new national screening programme called BowelScreen. In this section we want to find out about your future intentions to take part in BowelScreen.

Please answer all of the questions in this section by putting a '✓' in the boxes that apply to you.

F1. The following statements are about your decisions to take part in future bowel cancer screening. Please tell us how strongly you agree or disagree with each statement.
Please tick one box on each line

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
In the future I would *not* want to get tested for bowel cancer because.....					
The test might find something wrong	☐	☐	☐	☐	☐
It is too embarrassing	☐	☐	☐	☐	☐
It is inconvenient or too hard to schedule	☐	☐	☐	☐	☐
The stool test might be disgusting	☐	☐	☐	☐	☐
A special diet or emptying my bowel is too much trouble	☐	☐	☐	☐	☐
It might be painful	☐	☐	☐	☐	☐
I do not have symptoms	☐	☐	☐	☐	☐
It is too expensive	☐	☐	☐	☐	☐
There is no one to drive me home from the test	☐	☐	☐	☐	☐
It would be embarrassing to talk to my doctor about screening	☐	☐	☐	☐	☐
I do not have health insurance or a medical card	☐	☐	☐	☐	☐

In the future I <u>would</u> want to get tested for bowel cancer because.....	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Finding cancer early gives me a better chance at a cure	☐	☐	☐	☐	☐
Receiving clear findings would give me piece of mind	☐	☐	☐	☐	☐
Screening can find cancer early	☐	☐	☐	☐	☐
My family would be happy if I got screened	☐	☐	☐	☐	☐
Getting screened is part of taking care of myself	☐	☐	☐	☐	☐
If polyps are found and removed, cancer can be prevented	☐	☐	☐	☐	☐

I am very confident that I can....	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
make a decision about whether to get screened for bowel cancer	☐	☐	☐	☐	☐
complete bowel cancer screening	☐	☐	☐	☐	☐
complete bowel cancer screening even if I am nervous about it	☐	☐	☐	☐	☐
complete bowel cancer screening even if I are embarrassed about it	☐	☐	☐	☐	☐
complete bowel cancer screening even if I don't think I need it	☐	☐	☐	☐	☐
find time to complete bowel cancer screening	☐	☐	☐	☐	☐
talk to my doctor about bowel cancer screening	☐	☐	☐	☐	☐
complete any necessary preparation for bowel cancer screening	☐	☐	☐	☐	☐
get support from family and friends to help me complete bowel cancer screening	☐	☐	☐	☐	☐
complete bowel cancer screening even if I think my health is good	☐	☐	☐	☐	☐

Please write in the space below if you there is something else you would like to tell us about the bowel screening test

Thank you for taking the time to complete this survey

Please sign the consent form, and return it with this survey, in the enclosed pre-paid envelope to: PO BOX ADDRESS TO BE INSERTED.

Appendix D: Published papers

Clarke et al. BMC Gastroenterology 2014, 14:92
http://www.biomedcentral.com/1471-230X/14/92

BMC Gastroenterology

RESEARCH ARTICLE Open Access

Increasing late stage colorectal cancer and rectal cancer mortality demonstrates the need for screening: a population based study in Ireland, 1994-2010

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Abstract

Background: This paper describes trends in colorectal cancer incidence, survival and mortality from 1994 to 2010 in Ireland prior to the introduction of population-based screening.

Methods: We examined incidence (National Cancer Registry Ireland (NCRI) and mortality (Central Statistics Office) from 1994 to 2010. Age standardised rates (ASR) for incidence and mortality have been calculated, weighted by the European standard population. Annual percentage change was calculated in addition to testing for linear trends in treatment and case fraction of early and late stage disease. Relative survival was calculated considering deaths from all causes.

Results: The colorectal cancer ASR was 63.7 per 100,000 in males and 38.7 per 100,000 in females in 2010. There was little change in the ASR over time in either sex, or when colon and rectal cancers were considered separately; however the number of incident cancers increased significantly during 1994-2010 (1752 to 2298). The case fractions of late stage (III/IV) colon and rectal cancers rose significantly over time. One and 5 year relative survival improved for both sexes between the periods 1994-2008. Colorectal cancer mortality ASRs decreased annually from 1994-2009 by 1.8% (95% CI -2.2, -1.4). Rectal cancer mortality ASRs rose annually by 2.4% (95% CI 1.1, 3.6) and 2.8% (95% CI 1.2, 4.4) in males and females respectively.

Conclusions: Increases in late-stage disease and rectal cancer mortality demonstrate an urgent need for colorectal cancer screening. However, the narrow age range at which screening is initially being rolled-out in Ireland means that the full potential for reductions in late-stage cancers and incidence and mortality are unlikely to be achieved. While it is possible that the observed increase in rectal cancer mortality may be partly an artefact of cause of death misclassification, it could also be explained by variations in treatment and adherence to best practice guidelines; further investigation is warranted.

Keywords: Colorectal, Cancer, Ireland, Incidence, Survival, Mortality, Mass screening, Colon, Rectal

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Background

Over 1.23 million colorectal cancers are diagnosed worldwide annually [1] with 609 000 deaths [1]. Colorectal cancer is highly preventable if diagnosed early and treated. Screening has been available for many years through several modalities, including colonoscopy, sigmoidoscopy, and faecal-based tests [2-4]. Faecal-based tests, notably faecal occult blood testing (FOBT), are generally the route through which colorectal cancer screening programmes are being delivered internationally [5,6]. More recently faecal immunochemical testing (FIT) has been recommended for screening due to its improved sensitivity and specificity in detecting human haemoglobin and the fact that there is no need for test recipients to undergo dietary restrictions (which may be required for guaiac-based tests). Studies which have used FIT suggest improved uptake compared to other screening tests such as FOBT, possibly due to the absence of dietary restrictions, the need for fewer samples, absence of the need for storage if a one sample test, and ease of use [7]. However the authors state that these results are inconclusive and require further investigation from the patient's perspective [7]. Recent European and US guidelines recommend FIT as the initial screening test in population-based screening programmes [8,9].

Screening aims to detect colorectal disease either at a precancerous stage (when removal of polyps may prevent cancers developing) or when cancers are at an early stage (when treatment is more effective and patients may also benefit from improved quality-of-life). Screening therefore has the potential to reduce mortality, provided the service is of high quality and coverage is high [8].

Although many European countries have established screening programmes, until 2013, no programme was in place in Ireland. In 2009, a health technology assessment of population-based colorectal cancer screening found that biennial FIT at ages 55-74 would be considered the optimal screening strategy in Ireland in terms of potential for reducing incidence and mortality, and cost-effectiveness [10]. The National Cancer Screening Service launched BowelScreen, a national population-based programme, in December 2012. This paper aims to describe the population burden of colorectal cancer by examining trends in colorectal cancer incidence, mortality and survival during 1994-2010, prior to nationwide screening.

Methods

We examined incidence for 1994-2010 and mortality for 1994-2009 (2009 was the latest year for which mortality data was available at the time of the study). Information on incident cases was abstracted from the National Cancer Registry Ireland (NCRI). The NCRI records all cancers diagnosed in the population usually resident in Ireland through active case finding by tumour registration officers. The completeness of registration for all invasive cancers diagnosed to end 2008 was estimated to be over 97% [11].

The NCR has permission under the Health (Provision of Information) Act 1997 to collect and hold data on all persons diagnosed with cancer in Ireland. The use of that data for research is covered by the Statutory Instrument which established the Registry Board in 1991. All datasets were anonymised prior to analysis.

Site of tumour was recorded according to the International Classification of Diseases 10th revision (ICD10), and analysis included all primary invasive cancers of the colon (C18) and rectum (C19-C20) with a date of diagnosis during 01/01/1994 and 31/12/2010. For each diagnosed cancer, summary stage was derived from primary tumour (T), regional nodes (N) and distant metastasis (M) as recorded in pathology reports or, in the absence of these, from clinical staging, according to TNM 5th edition [12]. Where a patient was classified as MX ("distant metastases cannot be assessed"), the M category was defaulted to "M0" (no distant metastasis). For example, a patient with stage composite T3N1MX was treated as T3N1M0, stage III (Dukes C). Data on treatment received during the first year post-diagnosis was defined as planned first course of tumour directed treatment administered within one year of the diagnosis date (-30 to 365 days) and aimed at removing, destroying or preventing further tumour growth and included four treatment scenarios: (Surgery (Y/N), chemotherapy(Y/N), radiotherapy(Y/N), or not treated [ICD9CM and ICD10-AM]). Analyses of stage and treatment included cases diagnosed during 1995-2009, as this information was incomplete for 2010 cases and unreliable for 1994 cases, the first year of national registration. Colorectal cancer deaths (C18-20) were obtained from the Central Statistics Office (CSO) [13].

Age-standardised rates (ASR) for incidence and mortality were weighted by the European standard population using the direct method [14]. Trends presented as annual percentage change (APC) in ASRs of incidence (1994-2010) and mortality (1994-2009) were calculated using Joinpoint regression [15]. Joinpoint regression was also used to test for linear trends in treatment (1995-2009) and case fraction of early (stage I/II) and late (stage III/IV) disease (1995-2009). For descriptive purposes, age category percentages and treatment category percentages were given for three diagnostic periods: 1995-1999, 2000-2004 and 2005-2009.

In the Irish cancer registry, follow-up of cases is passive, where registered cancer cases are linked to death certificates provided by the CSO [16]. For survival analysis, the dataset was divided into three diagnostic periods: 1994-1998, 1999-2003 and 2004-2008. Survival time was censored at 31 December 2009 to ensure all cases had at least one year follow-up, and because this

was the latest date for which death ascertainment was complete. Our manuscript was drafted in late 2013, a point in time when we were confident that all deaths certificates from the CSO were matched to the cancer registry database. Cases which were preceded by another cancer (other than non-melanoma skin cancer) were excluded from survival analysis as were autopsy-only cases, death certificate only cases (DCO), colorectal cancers concurrent with other invasive malignancy and colorectal cancers diagnosed 2009-2010. Relative Survival (RS), the ratio of observed survival among a group of cases to the expected survival among the general population of the same age, sex and country, was computed based on deaths from all causes and using national life-tables [17].

Results

Incidence

The colorectal cancer ASR was 63.7 per 100,000 in males and 38.7 per 100,000 in females in 2010. There was little change in the ASR over time (Figure 1) in either sex, or when colon and rectal cancers were considered separately. However, the number of colorectal cancer cases in Ireland increased from 1752 in 1994 to 2298 in 2010, an annual rise of 2.1% (95% CI 1.8, 2.4; $p < 0.001$). The increase was somewhat higher in males (983 in 1994; 1343 in 2010; APC = 2.3%, 95% CI 2.0, 2.7) than females (769 in 1994; 955 in 2010; APC = 1.8%, 95% CI 1.4, 2.1).

In males, 62% of cases were in the colon; this was 71% in females. Increases in cases were observed in both colon (APC males = 2.6%, 95% CI 2.0, 3.2; APC females = 1.8%, 95% CI 1.4, 2.3) and rectal cancer (APC males = 1.9%, 95% CI 1.0, 2.4; APC females = 1.7%, 95% CI 1.4, 2.5).

Age distribution

Sixty nine percent of cases in males and 67% in females occurred in those aged ≥65; similar proportions in each sex were diagnosed aged 55-64 (males: 20%; females: 19%) and <55 (males: 11%; females: 14%). Over the three periods 1995-1999, 2000-2004 and 2005-2009 there was no change in the age distribution of either colon or rectal cancer in females or rectal cancer in males (data not shown).

Stage

During 1995-2009 early stage (I/II) colon cancers decreased by -1% annually in males (95% CI -1.8%, -0.1%) and in females by -0.7% (95% CI -1.4%, -0.1%). Conversely late stage (III/IV) colon cancers increased by 1.3% in males (95% CI 0.6%, 2.1%) and by 1.6% in females (95% CI 0.9%, 2.3%). Similarly early stage rectal cancers decreased by -2.1% (95% CI -2.8%, -1.4%) in males and -1.8% (95%

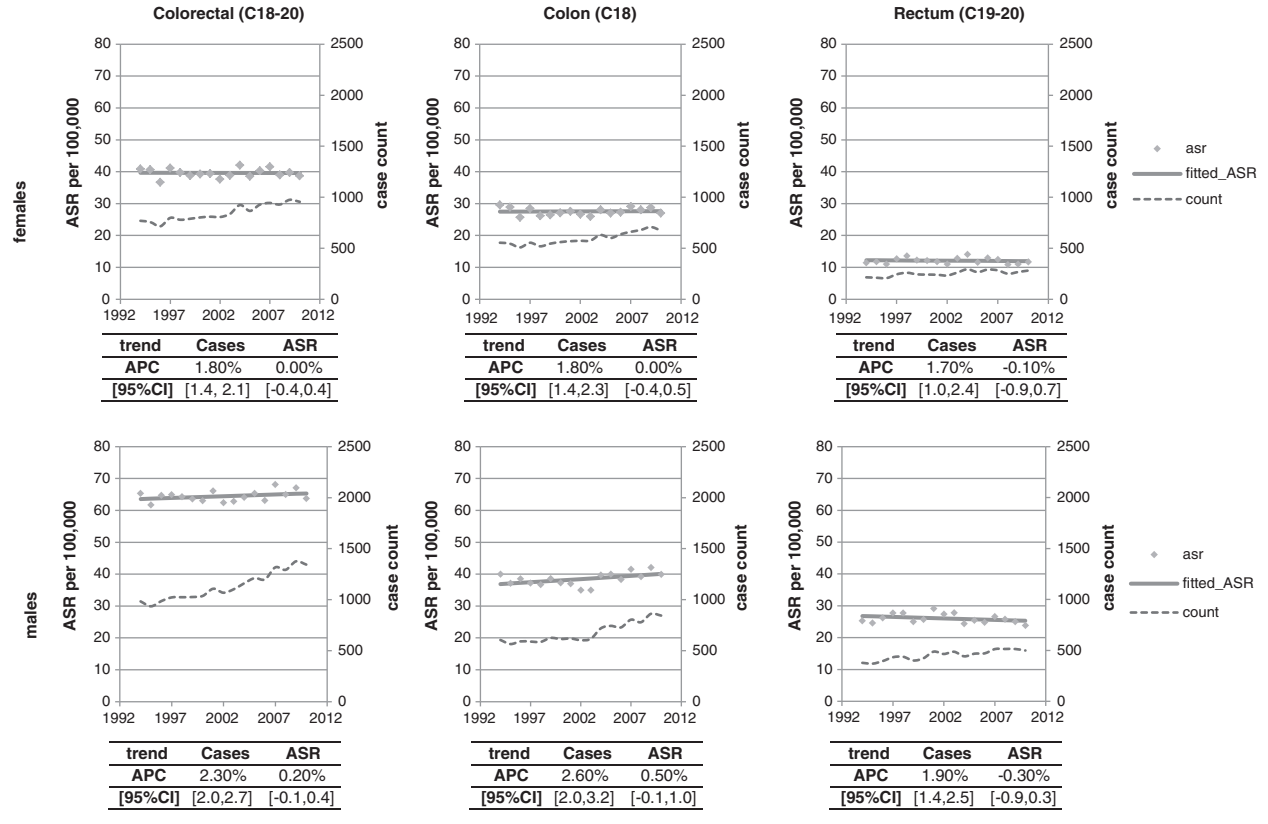


Figure 1 Age standardised incidence rate and incident cases of colorectal cancer by site of primary tumour and sex, 1994-2010.

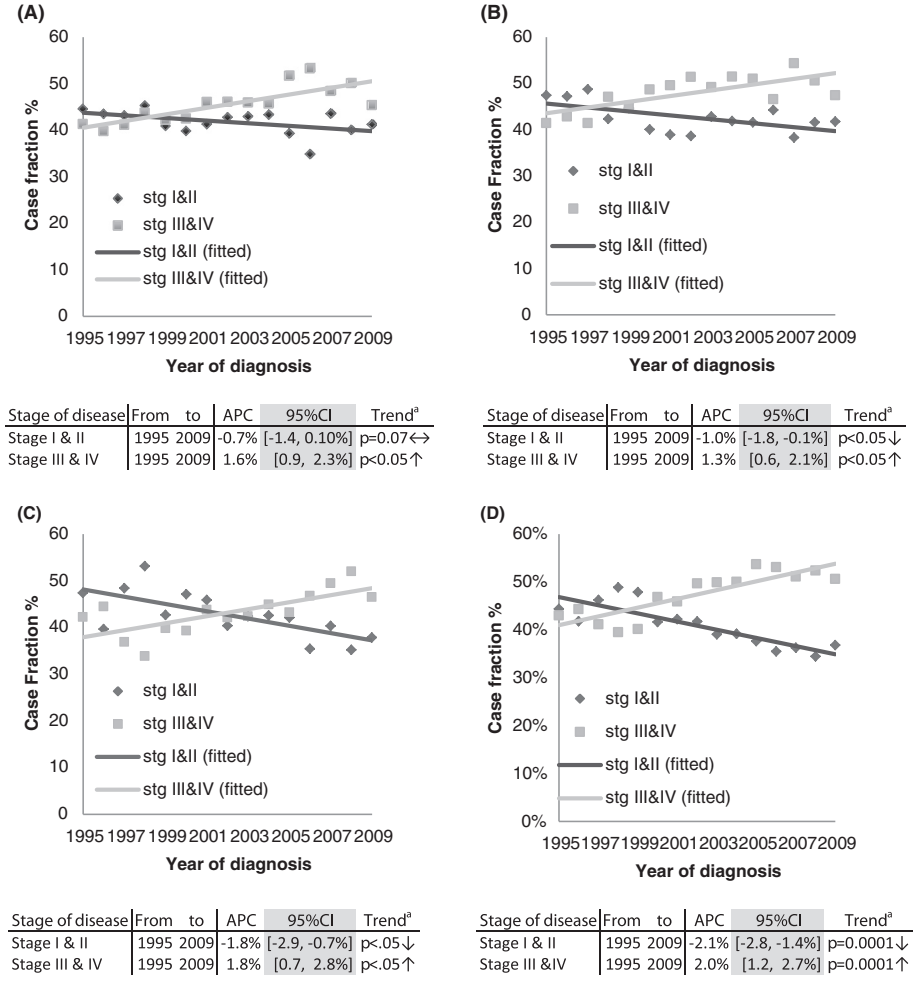
CI -2.9%, -0.7%) in females, while late stage disease increased significantly (males: APC = 2.0%, 95% CI 1.2%, 2.7%; females: APC = 1.8%, 95% CI 0.7%, 2.8%; Figure 2). Unstaged colon cancers decreased significantly in males by -2.2% (95% CI -4.1%, -0.2%; p-trend <0.05) and by -3.3% in females (95% CI -5.7%, -1.0%; p-trend < 0.05) annually. There was no significant change in unstaged rectal cancers in males (APC 0.6%, 95% CI -2.3%, 1.2%; p-trend = 0.5) or females (APC = 0.2%, 95% CI-2.3%, 2.8; p-trend = 0.8).

Treatment

Use of cancer-directed surgery (i.e. resection) for colon cancer increased from 76% in 1995-1999 to 79% in 2005-2009 (APC 0.3%, 95% CI 0.0, 0.6; p = 0.027), while for rectal cancer there was little change, remaining at 74% over the same period (APC -0.1%, 95% CI -0.5, 0.3; p = 0.54) (Figure 3). Use of chemotherapy for colon cancer rose significant from 21% in 1995 to 40% in 2006, thereafter levelling off to 38% up to 2009(APC = 5.7%, 95% CI 4.3, 7.1; p < 0.001). Similarly, in rectal cancer, chemotherapy use increased significantly from 22% in 1995 to 48% in 2002 (APC = 11.1%, 95% CI 8.7, 13.5; p < 0.001), reaching 49% by 2009 (Figure 3). Use of radiotherapy for rectal cancer increased significantly from 18% in 1995 to 37% in 2001, thereafter levelling off to just under 40% (APC 12.3%, 95% CI 9.1, 15.7; p < 0.001). The proportion of rectal cancer patients who received pre-surgery radiotherapy increased from 2% in 1995 to 13% in 2002 (APC 38.7%, 95% CI 28.7, 49.5; p < 0.001). Thereafter, the proportion receiving this combination increased at a slower rate from 18% in 2003 to 26% in 2009 (APC 9.9%, 95% CI 1.9, 18.4; p = 0.02) (Figure 3).

Survival

Relative survival improved over time for both sexes for colon and rectal tumours. From 1994-1998 to 2004-2008 1-year colon cancer survival in males increased by 8



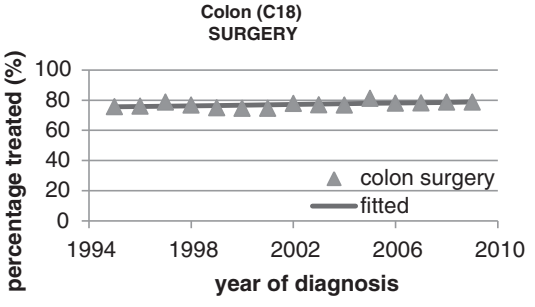
Stage of disease	From	to	APC	95%CI	Trend[a]
Stage I & II	1995	2009	-0.7%	[-1.4, 0.10%]	p=0.07↔
Stage III & IV	1995	2009	1.6%	[0.9, 2.3%]	p<0.05↑

Stage of disease	From	to	APC	95%CI	Trend[a]
Stage I & II	1995	2009	-1.0%	[-1.8, -0.1%]	p<0.05↓
Stage III & IV	1995	2009	1.3%	[0.6, 2.1%]	p<0.05↑

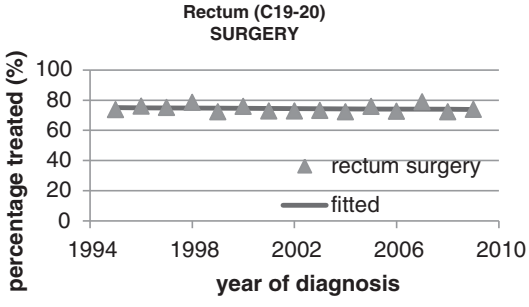
Stage of disease	From	to	APC	95%CI	Trend[a]
Stage I & II	1995	2009	-1.8%	[-2.9, -0.7%]	p<.05↓
Stage III & IV	1995	2009	1.8%	[0.7, 2.8%]	p<.05↑

Stage of disease	From	to	APC	95%CI	Trend[a]
Stage I & II	1995	2009	-2.1%	[-2.8, -1.4%]	p=0.0001↓
Stage III &IV	1995	2009	2.0%	[1.2, 2.7%]	p=0.0001↑

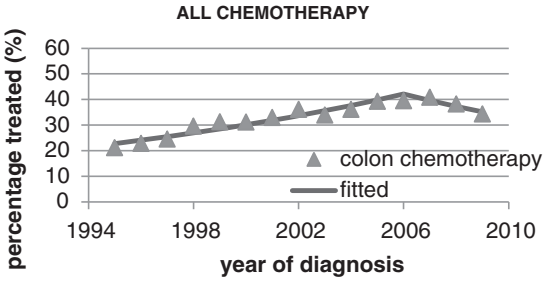
Figure 2 Case fraction for stage of disease at presentation, by gender and site of tumour for diagnostic period 1994-2009.
(A) COLON- FEMALES; **(B)** COLON MALES; **(C)** RECTUM- FEMALES; **(D)** RECTUM - MALES. [a]The p-value results are derived from a test of trend. The null hypothesis is that the APC = 0%: Alternative hypothesis is APC ≠ 0%. The APC is the slope of a log-linear regression curve from 1994-2009.



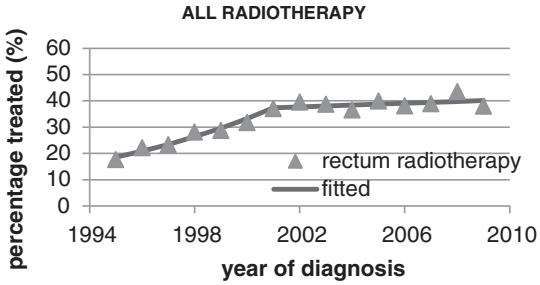
from	to	APC	95%CI	p-value
1995	2009	0.3	[0.0,0.6]	<0.05



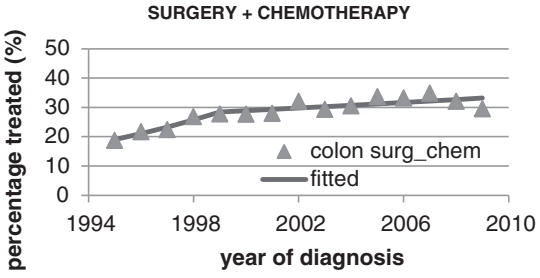
from	to	APC	95%CI	p-value
1995	2009	-0.1	[-0.5,0.3]	0.54



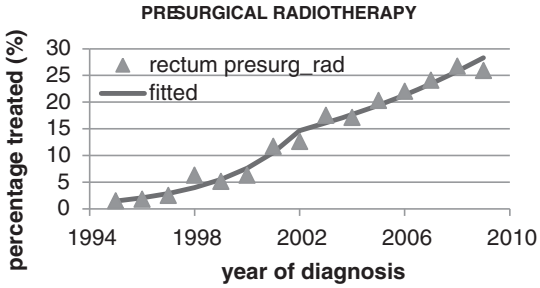
from	to	APC	95%CI	p-value
1995	2006	5.7	[4.3,7.1]	<0.001
2006	2009	-5.8	[-14.6,3.9]	0.20



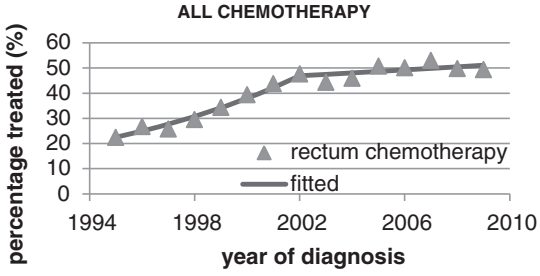
from	to	APC	95%CI	p-value
1995	20001	12.3	[9.1,15.7]	<0.001
2001	2009	0.9	[-1.0,2.8]	0.32



from	to	APC	95%CI	p-value
1995	1999	10.6	[3.6,18.1]	<0.001
1999	2009	1.5	[-0.1,3.2]	0.06



from	to	APC	95%CI	p-value
1995	2002	38.7	[28.7,49.5]	<0.001
2002	2009	9.9	[1.9,18.4]	0.02



from	to	APC	95%CI	p-value
1995	2002	11.1	[8.7,13.5]	<0.001
2007	2009	1.2	[-0.9,3.4]	0.23

Figure 3 Percentage of patients treated with various modalities 1995-2009.

percentage points to 77% (95% CI 75%, 78%), and in females by 5 percentage points to 73% (95% CI 71%, 75%). Five-year colon cancer survival increased by 8 percentage points to 58% (95% CI 56%, 61%) in males and by 7 percentage points to 59% (95% CI 56%, 62%) in females over the same time (Figure 4). One-year rectal cancer survival improved in males by 9 percentage points to 81% (95% CI 79%, 82%) and in females by 6 percentage points to 80% (95% CI 78%, 83%); 5-year rectal cancer survival in males improved by 9 percentage points to 55% (95% CI 52%, 59%) and in females by 9 percentage points to 61% (95% CI 57%, 65%; Figure 5).

Mortality

In 2005-2009, on average 400 females (255 colon; 145 rectum) and 552 males (313 colon; 239 rectum) died from colorectal cancer annually. Colon cancer deaths declined over time in both sexes (males: 360 in 1994; 302 in 2009; APC = -1.7%, 95% CI -2.4%, -1.0%; females: 321 in 1994; 240 in 2009; APC = -2.1%, 95% CI -3.0%, -1.2%). Rectal cancer deaths rose significantly in males from 148 in 1994 to 262 in 2009 (APC = 4.6%, 95% CI 3.4%, 5.9%) and in females from 94 in 1994 to 141 in 2002 (APC = 4.4%, 95% CI 3.0%, 5.9%).

Colorectal cancer age-standardised mortality rates (ASR) decreased by -1.8% (95% CI -2.2%, -1.4%) annually during 1994-2009. Colon cancer ASRs fell in both sexes (males: APC = -3.7%, 95% CI 4.4%, -3.0%; females: APC = -4.2%, 95% CI -5.1%, -3.2%), but rectal cancer ASR (mortality) rose (males: APC = 2.4%, 95% CI 1.1%, 3.6%; females: APC = 2.8%, 95% CI 1.2%, 4.4%; Figure 6).

Discussion

Over the past 20 years the number cases of colorectal cancer has increased significantly in Ireland; however once adjusted for changes in the age distribution of the population over time the rate has remained stable. Internationally colorectal cancer rates have stabilised in economically developed countries and Ireland is no exception in this regard [18]. In comparison to other European countries, in 2008 Ireland had a higher incidence rate than the EU average and 23% higher than the rate in the United Kingdom [19]. In the European region incidence has increased in males at a greater rate than female incidence during the period 1988 to 2008 [20]. Survival was just below the EU average but similar to the United Kingdom [21]. The improvements in survival reported in this paper were also seen in other European countries during the 1990s and early 2000s [21]. European 5 year survival of colon cancer increased from 54.2% in the period 1999-2001 to 58.1% in 2005-2007, and from 52.1% to 57.6% for rectal cancer over the same period [22]. Although Irish survival improved, it is still lower than the European average [22]. Our data indicates that survival continued to improve for cases diagnosed during 2005-2009. While we did not have detailed information on the dose and intensity of chemotherapy and radiotherapy regimens, better uptake in and application of treatment options during 1995-2009 correlate with the improvement in survival.

Stage

One of the striking findings of this study was that almost half of cases had relatively late stage at diagnosis (stage III/IV) and, over the period under investigation, the proportion with stage III/IV disease increased from 42% to 50%. The increase in stage III/IV cancers is likely to be as a result of more comprehensive investigation in the peri-operative period, with improvements in imaging and diagnostic methods, resulting in a significant shift in stage allocation from stage I/II to stage III/IV over

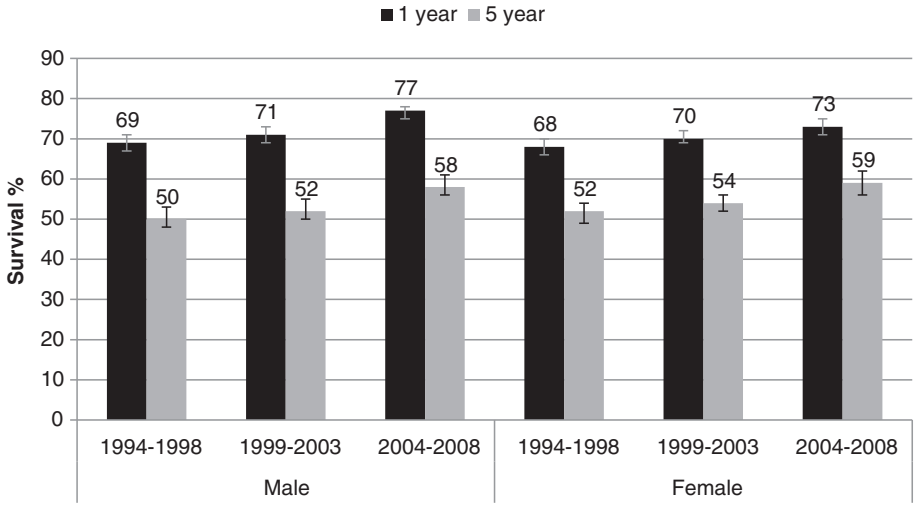


Figure 4 One and five year relative survival for colon cancer for diagnostic periods by sex with 95% confidence intervals.

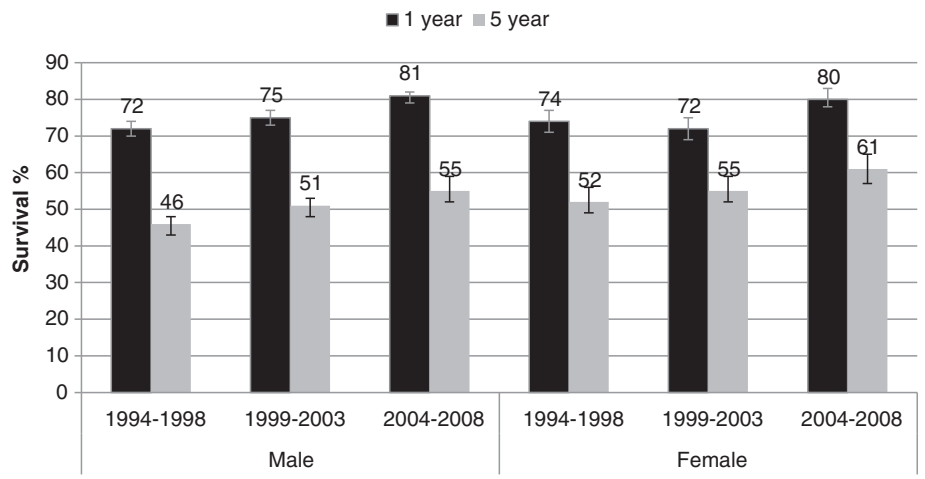


Figure 5 One and five year relative survival for rectal cancer by diagnostic period by sex, with 95% confidence intervals.

the years 1995-2009. Another possibility is that the number of nodes taken at resection increased over the period 1995-2009, thereby leading to a situation where the probability of finding a positive node(s) increased commensurately, which would have tipped the balance in favour of stage III/IV over stage I/II according to UICC-TNM, 5th edition. However, we do not have details on node count to support this hypothesis. This question will be addressed in a more comprehensive study of stage migration in colorectal cancer at this registry.

If effective, screening has the potential to change the stage distribution of colorectal cancer in the population. As regards FIT-based screening, which is being implemented

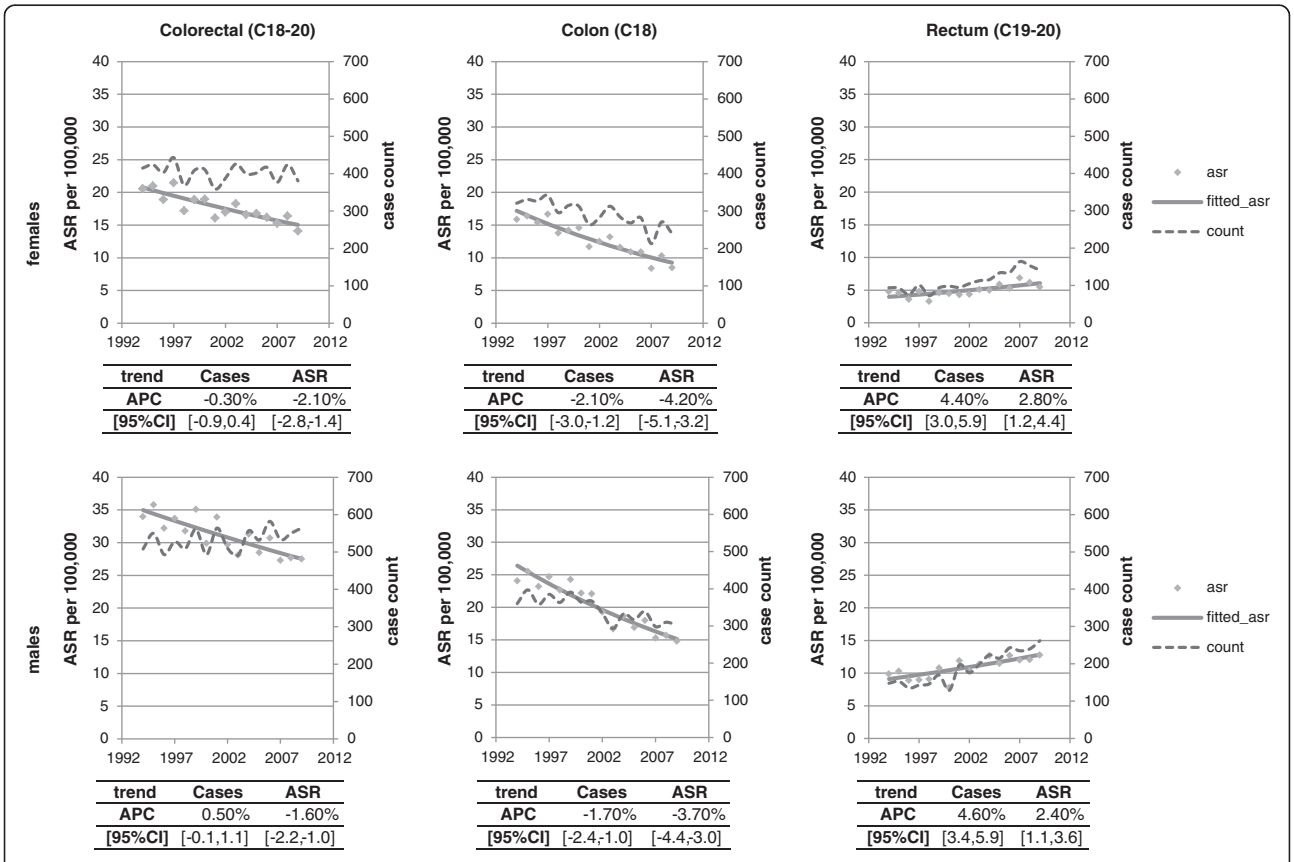


Figure 6 Age standardised mortality rate and number of deaths for colorectal cancer by site of primary tumour and sex, 1994-2009.

in Ireland, Cole et al reported that colorectal cancers were detected at significantly earlier stages in those invited to participate in a screening programme using FIT [23]. In a health technology assessment for Ireland, it was estimated that, by year 10 of a programme, the percentage of cases diagnosed at stages I/II would increase from 46% to 53% and stages III/IV decrease from 54% to 47% [10]. These estimates were based on screening targeted at those aged 55-74 with a best case scenario uptake of 53% (based on the UK experience of FOBT screening) [24]. Similar uptake has been achieved in pilot FIT screening in Ireland [25]. The BowelScreen programme, which has recently commenced, is initially inviting individuals aged 60-69. While the stated intention is to eventually include 55-74 year olds, this is likely to take a number of years due to the development of colonoscopy capacity. Therefore the estimates of potential reductions in late stage disease are very unlikely to be achieved by year 10 of the programme.

Mortality

In 2008 Ireland ranked midway of 30 European countries in relation to mortality, similar to the EU average but marginally higher than the United Kingdom [19]. Annual decreases in age standardised mortality rates for colorectal cancer in males and females were observed in this study. However this concealed significant increases in the mortality rate for rectal cancers of 2.4% in males and 2.8% in females. Scrutiny of European data reveals that most countries have experienced static mortality rates over the past 15-20 years. However a few, in addition to Ireland, have described increases. These include Spain, with an APC of 3.5% during 1994-2005, Malta with an APC of 5.2% during 1994-2008 and among selected registries in Germany with an APC of 17.1% during 1998-2007 [26]. In terms of potential explanations for these trends, the first that must be considered is whether it might be an artefact of coding of rectal cancer deaths. We have shown that there was a significant decline in the annual death rate for pooled colorectal sites. Yet, there was a steeper decline in the rate of colon deaths, with a compensatory increase in the rate for 'rectum' deaths. This suggests that there may have been a subtle shift in death certificate coding allocation from 'colon' to 'rectum' over the period we have examined. It has long been recognised that physicians tend to report non-specific cancer sites on death certificates; thus, if physicians change how they record cause of death on the death certificate over time, this may induce an apparent change in mortality rates [27]. In 1981, Percy et al reported that misclassification led to over reporting of colon cancer deaths and underreporting of rectal cancer deaths [27]. More recently, in the US, Yin et al reported inaccurate coding of underlying cause of death, with the vast majority of misclassifications being colon cancers incorrectly classified as rectal cancers [28]. Further investigation is warranted to explore the extent and nature of misclassification on death certificates in European countries in recent years, perhaps comparing countries with rising and static rectal cancer mortality rates.

Another possible explanation of the observed increase in rectal cancer mortality is patterns in treatment utilisation. Pre-operative radiotherapy has been recommended for resectable rectal cancer in recent years [29,30] and in line with this the proportion who received pre-operative radiotherapy has increased markedly since 2000, in Ireland and in other countries [31]. However Carsin et al have reported low use of radiotherapy in Ireland (27%) [31] compared to US and EU populations (46%-62%) [32-34]. Moreover, although data from trials suggests that pre-operative use is more effective, a significant proportion treated with radiotherapy in Ireland receive it post-operatively rather than pre-operatively [31]. These observations raise the possibility that underuse of radiotherapy, particularly preoperative radiotherapy, may be a contributor to rectal cancer mortality trends. Moreover, while the current study found that radiotherapy use was continuing to rise, any impact of this on mortality rates will not be seen for several years.

In terms of surgery, evidence-based guidelines have been published in Ireland aimed at standardising surgical management of rectal cancer [30]. An audit of all rectal cancers diagnosed in 2007 found that, while guidelines were in place, best practice was frequently not adhered to [35]. Surgery for rectal cancer can result in significant morbidity if undertaken without appropriate and accurate pre-operative staging. Accurate localisation of the tumour [36-38], use of MRI (magnetic resonance imaging) [39] and ERUS (Endo-rectal ultrasound) [40-42] as diagnostic tools, and recording of accurate pre-operative histological data [43,44], are all essential for successful treatment. However the national audit revealed that there were often inadequate investigations and/or recording of such data [35]. In addition while multi-disciplinary meetings (MDM) have been shown to improve outcomes for rectal cancer [45,46], treatment options were only discussed at MDMs for around half of patients. Moreover patients treated at low volume centres were less likely to be discussed at MDMs and to have neo-adjuvant therapy [35]. Further evidence suggests that comorbidity, rather than age, in elderly rectal cancer patients increases risk of death after surgery [47]. Therefore age alone should not dictate the use of restorative rectal resection [47]. However, our analyses indicate lower use of surgery in elderly than younger patients (≥75; 81%; <75: 92-99%) as well as larger increases in age standardised mortality in those aged 70 and older [13]. These observations, combined with

likely under use of best practice, may provide a possible explanation for the observed trends in mortality.

Biennial FIT-based screening in the 55-74 age group in Ireland could reduce colorectal cancers deaths in the population from as early as the second year of the programme [10]. However, as noted earlier, screening is being introduced in those aged 60-69, suggesting that it is likely to take some considerable time to have any impact on the trends in rectal cancer mortality reported here.

Conclusion

Age standardised incidence has remained static in Ireland over the period 1994-2010, but 1-year and 5-year survival continues to increase in both sexes. The proportion of cases with late stage disease has increased over time, as have mortality rates for rectal cancer. These trends indicate the need for efficient and timely roll-out of BowelScreen. However the narrow age-range at which BowelScreen will operate in the first instance means that the potential benefits of screening, in terms of more advantageous stage distribution and reductions in colorectal cancer incidence and mortality in the population, are unlikely to be achieved in the short-term.

Competing interests

The authors declare that they have no completing interests.

Authors' contributions

NC contributed to interpretation and drafted the manuscript. JMcD carried out statistical analysis. LS conceived of the study and advised on analysis and interpretation. PK advised on analysis and interpretation. JMcD, LS and PK commented on drafts of the manuscript. All authors approved the final version.

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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Comparison of Uptake of Colorectal Cancer Screening Based on Fecal Immunochemical Testing (FIT) in Males and Females: A Systematic Review and Meta-analysis

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Abstract

Background: Colorectal cancer is the third most common cancer in males and the second in females worldwide. Incidence and mortality are higher in men than women. Colorectal cancer screening is effective in reducing mortality. Internationally, fecal immunochemical testing (FIT) is increasingly being recommended as the primary screening test. This systematic review and meta-analysis aimed to determine whether uptake of FIT screening differs between men than women.

Methods: We searched PubMed and Embase for peer-reviewed articles published in English during 2000–2013 for randomized controlled trials (RCT) or observational studies of screening using FIT that quantified numbers invited and participating by gender. Meta-analysis was performed using a random effects model.

Results: Six hundred and eighty-five citations were identified, 19 meeting the inclusion criteria. Random effects meta-analysis found male uptake was significantly lower than female uptake [odds ratio (OR), 0.84; 95% confidence interval (CI), 0.75–0.95; $P < 0.01$]. This generally persisted throughout subgroup analysis of study design (RCTs vs. observational studies and study quality), screening organization (methods of invitation, number of samples, age range of screening, recommendations, and reminders), and setting.

Conclusions: Meta analysis of FIT screening studies indicates significantly lower uptake among men.

Impact: Further investigation is required into factors influencing acceptability and participation of FIT screening in both sexes.

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Introduction

Colorectal cancer is the third most common cancer diagnosed in males and the second most common in females (1). Worldwide more cases and deaths occur in males than females, with the age-standardized incidence rate 44% higher (20.6 vs. 14.3 per 100,000) and age-standardized mortality 45% higher in males (10.0 vs. 6.9 per 100,000; ref. 1). Most colorectal cancers are considered to arise from precancerous polyps; if left *in situ* polyps can progress to cancer over a 10- to 15-year period (2). However, colorectal cancer can be prevented, or treated effectively if detected early, through screening (3). Evidence indicates efficacy of screening in reducing cancer mortality and, in some instances, incidence (4–8).

A number of countries have implemented population-based colorectal cancer screening programs (9–11). Screening can be delivered through procedures conducted in a clinic or doctor's office, such as colonoscopy or flexible sigmoidoscopy (FS), or through noninvasive methods that are suitable to be undertaken in an individual's home, such as fecal occult blood testing (FOBT) or fecal immunochemical testing (FIT). Currently, most programs that use fecal-based tests use FOBT (11, 12). However, FIT is a more specific and sensitive test (8) and recent guidelines recommend it as the initial screening modality (3, 13). In order for a screening program to be effective in reducing mortality it needs to be well organized and requires high uptake (3). It is well established that uptake is higher for noninvasive, than more invasive, colorectal cancer screening tests (14). In addition, recent evidence suggests uptake is higher with FITs than FOBTs (15). Furthermore, some studies suggest gender differentials in uptake; uptake is higher among men for more invasive procedures and higher among women for noninvasive tests (16–18). What remains to be established is whether there is gender difference in uptake of screening based on FIT.

The aim of this study was to conduct a systematic review and meta-analysis to determine whether uptake of FIT-based screening differs by gender. A secondary aim of the study was to assess factors that may influence any gender-based differences.

Materials and Methods

Search strategy and selection criteria

Citations published in peer-reviewed English journals during January 2000 to December 2013 that reported uptake of FIT-based screening in males and females, were identified from Pubmed and Embase using a structured search strategy. MeSH terms included "neoplasms," "malignancy," "early detection of cancer," "compliance," "adherence," "colon" and "rectum." Text word search

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terms included variations of "colorectal," "bowel," "colon," "rectal," "gastric," "cancer," "neoplasm," "malignant," "participation," "compliance," "uptake," "attendance," "FIT," "fecal," "fecal," "immunochemical," "test," "kits," "FOBT," "iFOBT," "occult," "blood," and "test." One author (N. Clarke) carried out the initial screening from the search strategy to remove ineligible citations such as duplicates, conference proceedings, letters, commentary, and editorials. Two authors (N. Clarke and A. Osborne) then independently determined eligibility based on the inclusion and exclusion criteria by reading the full text of the remaining articles. To be included in the review, FIT was required to be used as a primary screening (i.e., initial) test; studies in which FIT was used for triage of people with a positive primary screening test (e.g., FIT following gFOBT) were excluded. Studies which offered individual participants a choice of different screening tests, such as FIT or colonoscopy (i.e., in which the participant decided which test to undergo) were excluded. Studies or trials with a single group/test or multiple arms/tests and in which the screening test was assigned by the investigator were eligible for inclusion. In those with multiple arms, FIT had to be the primary test in at least one arm and only the arm(s) using FIT were included in the analysis. Studies were included if they reported: randomized controlled trials (RCT—experimental studies in which individuals are randomly allocated to receive or not receive an intervention and then followed to determine the effect of the intervention) in which one arm involved screening by FIT; observational studies (study designs that are not randomized control trials) in which FIT was the primary screening test; or screening programs in which FIT was the primary screening test. Studies were included if they reported numbers of people invited and screened by FIT by gender. Differences of opinion on study eligibility were resolved through discussion among the authors. A standardized form was developed to abstract data from eligible studies, including invitation and uptake figures by gender, study design, screening age range, invitation and recruitment methods, use of recommendations and reminders, and number of samples required.

Quality assessment

Eligible studies were assessed for methodologic quality using two instruments: the Cochrane risk of bias tool (19) for RCTs and the Newcastle–Ottawa Scale for observational studies (20). The Cochrane risk of bias tool assesses bias on six domains covering selection, performance, detection, attrition, reporting, and any other bias. For our review, we assessed only selection bias (random sequence generation), reporting, and other bias (comparability of confounding factors and appropriate use of statistical tests). Assessments of performance and detection bias were not carried out as many screening trials are unblinded; it is therefore likely that participants are aware of the arm to which they are assigned (21). Attrition bias or incomplete outcome data (including nonresponse, noncompliance or withdrawal) was not assessed because noncompliance was the outcome of interest. Cohort (study of groups of individuals, some of whom are exposed to an intervention and followed over time to determine the effect of the intervention on the outcome of interest) and cross-sectional studies (observation of a defined population at a single point in time or during a specific time interval where outcome and exposure are determined simultaneously) were assessed using the Newcastle–Ottawa Scale by awarding stars as an overall rating of three methodologic factors: selection [sample representativeness (1 star) and sample size (1 star)], comparability [authors controlled for or reported confounding factors for uptake by sex and age (1 star), and for other factors such as education, marital, income, or employment status (1 star)] and outcome [clear description of statistical analysis (1 star) and measurement of association or difference with confidence intervals (CI) and *P* values and use of appropriate statistical test (1 star)]. After risk of bias assessment, RCTs were also assessed for quality using the same criteria as observational studies. Studies were assessed overall based on the number of stars they had been awarded of a possible six, with 5 to 6 stars being considered high quality, 3 to 4 stars moderate quality, and 2 or less stars low quality.

Statistical methods

Within each study, participants were invited to complete one test. Studies that compared screening tests (multiple arms in RCTs) did not offer more than one choice of screening to each participant. Uptake was defined as the number of persons targeted (i.e., persons invited to participate in screening) who returned a completed FIT kit.

Studies were combined in a meta-analysis, conducted in Review Manager 5 (The Cochrane Collaboration). Because of the high level of heterogeneity, a random effects model was used. Subgroup analysis was also carried out to determine whether the effect estimates varied by study characteristics. Subgroups were defined on the basis of study quality (high, moderate, or low), study design (RCT or observational), age range of those invited to screening (40–75, 50, or older with no upper age limit), number of FIT samples required for test completion (1 or 2 or more samples), letter of invitation (with advance notification or without advance notification), test delivery method (test mailed to recipient or test collected by recipient), use of recommendations or endorsement of test (yes or no), and use of reminders (reminder provided or no reminder provided). Studies that did not report on these methods or that used different methods were excluded from relevant analysis. Only one study reported multiple screening rounds. This study (22) was very large (comprising 92% of the invited population and 87% of the screened population when all studies were combined) and reported six screening rounds (22). In the primary analysis, this study was included with data from 2004 (round 1). Six sensitivity analyses were conducted to determine their impact on the effect estimate: (i) excluding this study entirely; (ii) using round 2 data (2005), (iii) using round 3 data (2006), (iv) using round 4 data (2007), (v) using round 5 data (2008), and (vi) using round 6 data (2009).

Results

Study selection and characteristics

In total, 685 potentially eligible citations were identified. Following review, 19 studies were eligible for inclusion in the review and meta-analysis (22–40). A flow chart of the search strategy results is provided in Fig. 1. Study characteristics are summarized in Table 1. Six were RCTs, 12 were cross-sectional studies, and one was a cohort study. Nine studies originated from Europe, three from Asia, three from North America, three from Australia, and one from South America. Fifteen studies were population-based (i.e., studies in which screening is systematically offered by invitation to a defined population).

Across the 19 studies, a total of 2,650,358 [round 1; Park and colleagues (22)] individuals were invited to participate in FIT

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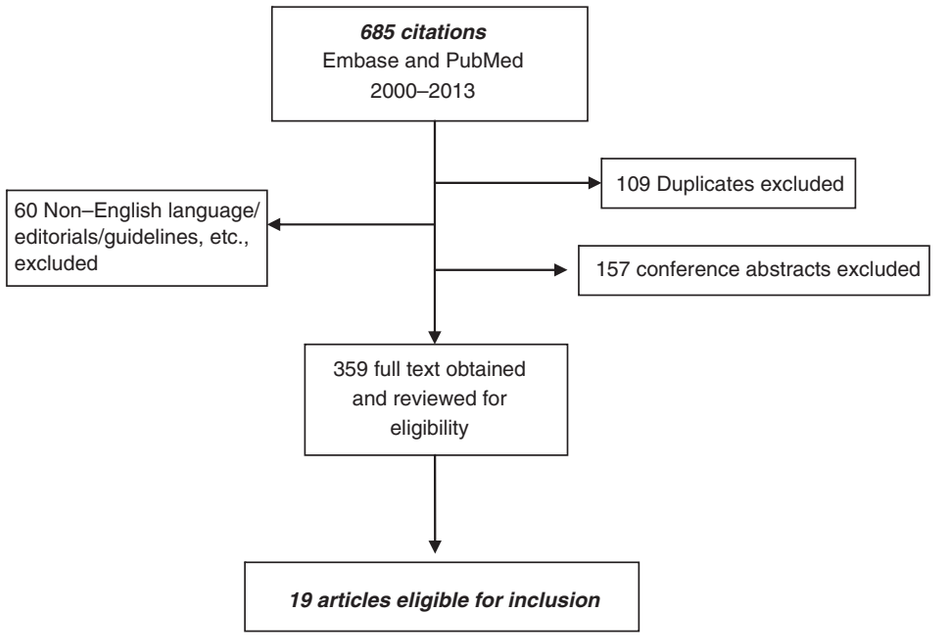

Figure 1.
Study flow diagram: result of search strategy.

screening and 407,451 were screened (uptake = 15.4%). Excluding the largest study (22), 384,979 were invited and 169,586 screened (uptake = 44.1%).

Meta-analysis

Uptake in males and females combined ranged from 11% (round 1; ref. 22) to 90% (Table 2; ref. 26). Meta-analysis of all included studies indicate significantly lower male uptake [odds ratio (OR), 0.84; 95% CI, 0.75–0.95; $P < 0.01$; Fig. 2).

Park and colleagues (22) account for 85% (round 1; round 2: 92%) of the entire screening population in the meta-analysis. In round 1 of this study, uptake was significantly higher in males than females (OR, 1.16; 95% CI, 1.15–1.17; $P < 0.01$; Table 2), while in the subsequent five rounds uptake was significantly lower in males than females (Table 2).

When the meta-analysis was repeated replacing the round 1 results of Park and colleagues (22) with those from each of the subsequent five rounds, this had little impact on the overall risk estimate which ranged between 0.83 and 0.84 (round 2: overall meta-analysis OR, 0.84; 95% CI, 0.77–0.90; $P < 0.01$; round 3: overall meta-analysis OR, 0.83; 95% CI, 0.77–0.90; $P < 0.01$; round 5: overall meta-analysis OR, 0.83; 95% CI, 0.77–0.90; $P < 0.01$; and round 6: overall meta-analysis OR, 0.83; 95% CI, 0.77–0.90; $P < 0.01$). When Park and colleagues (22) was excluded entirely from the meta-analysis, male uptake remained significantly lower (OR, 0.83: 95% CI, 0.74–0.92; $P < 0.01$).

Quality assessment

Of the 19 studies, seven were deemed to be of low quality, and 12 were considered moderate quality, while none were deemed to be of high quality. Results are summarized in Table 3. Moderate quality studies had significantly lower uptake in males (OR, 0.81; 95% CI, 0.76–0.85; $P < 0.01$) while low-quality studies had nonsignificantly lower uptake in males (OR, 0.89; 95% CI, 0.63–1.26; $P = 0.51$); however, there was no significant difference in these subgroups ($P = 0.58$; Table 4). In addition, we repeated the meta-analysis restricted to moderate quality studies only; the lower uptake in males persisted and the effect size was very similar to that seen when all studies were included (moderate quality studies only: OR, 0.83; 95% CI, 0.71–0.96; $P = 0.01$).

Study design

Uptake was significantly lower in males than females in both RCTs (OR, 0.83; 95% CI, 0.71–0.97; $P = 0.02$) and observational studies (OR, 0.83; 95% CI, 0.76–0.91; $P < 0.01$; Table 4). There was nonsignificantly lower male uptake in studies which were not part of an organized screening program (OR, 0.74; 95% CI, 0.51–1.07; $P = 0.11$) as was the case for studies which were not population-based (OR, 0.88; 95% CI, 0.73–1.07; $P = 0.20$).

Setting

Uptake was significantly lower among males in studies based in Europe and Australia, nonsignificantly lower in studies based on North America and South America, and not different in studies based in Asia (Table 4) but, overall, subgroup differences for setting were nonsignificant ($P = 0.16$).

Letter of invitation

The recruitment methods used in the 16 studies that described this were heterogeneous. Invitations were made from a central screening location ($n = 10$), general practitioner (GP) clinics ($n = 4$), or through an index subject invited for cervical cancer screening ($n = 1$; Table 1). Nine studies used a letter of invitation mailed to subjects while three studies used an advance notification letter of invitation, mailing letters to inform subjects they would be invited, and subsequently mailing a letter of invitation to participate. One study used an advanced notification letter inviting subjects to complete a bowel cancer survey, subsequently mailing a test to responders. Subgroup differences for invitation methods were nonsignificant ($P = 0.41$). Male uptake was significantly

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Table 1. Characteristics of the 19 studies on FIT uptake in males and females included in the meta-analysis

Study & year	Population based	Age range, y	Letter of invitation	Test delivery method	Recruitment location	Recommendation/ endorsement	Reminder	Number of samples and interval	Test	Country
Cohort studies										
Senore et al., 2012 (33)	Yes	58 and 60	Letter—no advance notification	Test collected	GP	GP	No reminder	1	OC Sensor	Italy
Cross-sectional studies										
Fenochi et al., 2006 (26)	No	50+	Not reported	Test collected	GP	GP	2-mo reminder	1	OC Hemodia	Uruguay
Gregory et al., 2011 (32)	Yes	50–74	Advance notification letter to screening survey	Test mailed	Central	No recommendion	6-wk reminder	Not reported	InSure	Australia
Kluhsman et al., 2012 (38)	No	50+	Face to face rec ruitment	Test collected	GP	GP	2 wks	Not reported	INSure	United States
Crotta et al., 2004 (25)	Yes	50–74	Letter—no advance notification	Test collected	Central	Mayor	2-mo reminder	1	OC Sensor, Japan	Italy
Chen et al., 2007 (27)	Yes	50+	Not reported	Test collected	Out-reach	Public health nurse	Not reported	1	Not reported	Taiwan
Parente et al., 2009 (29)	Yes	50–69	Letter—no advance notification	Test collected	Central	No recommendion	No reminders	1	HM-Jack	Italy
Levy et al., 2010 (30)	No	50–64	Advance notification letter	Test mailed	Central	No recommendion	Not reported	Not reported	Clearview ULTRA FOB	United States
Park et al., 2011 (22)	Yes	50+	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Republic of Korea
Cai et al., 2011 (31)	Yes	40–74	Not reported	Not reported	Not reported	Not reported	Not reported	2 at interval of 1 week	Not reported	China
Ferrari et al., 2012 (36)	Yes	50–69	Not reported	Not reported	Not reported	GP	Reminder - interval not reported	Not reported	Tes t tube	Italy
McDonald et al., 2012 (37)	Yes	50–74	Letter—no advance notification	Test mailed	Central	No recommendion	Not reported	1	Eiken	Scotland
Kelley et al., 2013 (40)	Yes	50–75	Letter—no advance notification	Test mailed	Not reported	Not reported	Not reported	2 at interval of 1 day	OC Sensor	Ireland
Randomized control trials										
Cole et al., 2002 (23)	No	50+	Letter—no advance notification	Test mailed	Central & GP	No recommendation/ practice/GP	6-wk reminder	3 interval not reported	Flexsure OBT	Australia
Cole et al., 2003 (24)	Yes	50–69	Letter—no advance notification	Test mailed	Central	No recommendion	6-wk reminder	3 (FlexSure OBT) interval not reported 2 (Insure) Interval not reported	FlexSure OBT/ InSure	Australia
Gupta et al., 2013 (39)	Yes	54–64	Letter—no advance notification	Test mail ed	Central	No recommendion	3-wk reminder	1	O C -Auto FIT C HEK	United States
Hol et al., 2012 (34)	Yes	50–74	Advance notification letter	Test mailed	Central	No recommendion	6-wk reminder	1	OC Sensor	the Netherlands
Quintero et al., 2012 (35)	Yes	50–69	Advance notification letter	Test collected	Central	GP/specialist	3- and 6-mo reminders	1	OC Sensor	Spain
van Rossum et al., 2008 (28)	Yes	50–75	Letter—no advance notification	Test mailed	Central	No recommendion	2-wk reminder	1	OC Sensor	the Netherlands

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Table 2. Uptake figures by male and female for the 19 studies in meta-analysis with ORs, 95% CI, and *P* value

	Total		Males		Females			
	Invited	Screened	Invited	Screened	Invited	Screened		
Author/year	*n*	*n* (%)	*n*	*n* (%)	*n*	*n* (%)	OR (95% CI)	*P*
Park et al., 2011 Round 1 (22)	2,265,379	237,865 (10.5%)	969,813	105,710 (10.9%)	1,295,566	123,148 (10.2%)	1.16 (1.15–1.17)	$P < 0.05$
Park et al., 2011 Round 3 (22)	4,406,700	691,754 (15.7%)	2,062,961	307,381 (14.9%)	2,343,739	384,373 (16.4%)	0.89 (0.89–0.90)	$P < 0.05$
Park et al., 2011 Round 6 (22)	4,625,557	1,211,896 (26.2%)	2,150,635	535,508 (24.9%)	2,474,922	675,654 (27.3%)	0.88 (0.88–0.89)	$P < 0.05$
Cole et al., 2002 (23)	2,400	857 (35.7%)	1,094	375 (34.2%)	1,306	482 (36.9%)	0.89 (0.75–1.05)	$P = 0.18$
Cole et al., 2003 (24)	1,212	425 (35.1%)	592	196 (33.1%)	620	229 (36.9%)	0.85 (0.67–1.07)	$P = 0.33$
Crotta et al., 2004 (25)	2,961	1,631 (55.1%)	1,403	710 (50.6%)	1,558	921 (59.1%)	0.71 (0.61–0.82)	$P < 0.05$
Fenocchi et al., 2006 (26)	11,734	10,573 (90.1%)	3,663	3,282 (89.6%)	8,071	7,291 (90.3%)	0.92 (0.81–1.05)	$P = 0.22$
Chen et al., 2007 (27)	56,968	22,672 (39.8%)	21,502	9,481 (44.1%)	35,466	13,191 (37.2%)	1.33 (1.29–1.38)	$P < 0.05$
van Rossum et al., 2008 (28)	10,322	6,157 (59.6%)	5,037	2,820 (55.9%)	5,285	3,337 (63.1%)	0.74 (0.69–0.80)	$P < 0.05$
Parente et al., 2009 (29)	78,083	38,693 (49.6%)	37,838	18,314 (48.4%)	37,950	20,379 (53.7%)	0.81 (0.79–0.83)	$P < 0.05$
Levy et al., 2010 (30)	297	235 (79.1%)	131	131 (80.9%)	166	129 (77.7%)	1.22 (0.69–2.15)	$P = 0.50$
Cai et al., 2011 (31)	31,963	24,409 (76.4%)	16,169	11,962 (74.0%)	15,794	12,447 (79.0%)	0.76 (0.73–0.81)	$P < 0.05$
Gregory et al., 2011 (32)	375	192 (51.2%)	181	86 (47.5%)	194	106 (54.6%)	0.75 (0.50–1.13)	$P = 0.17$
Senore et al., 2012 (33)	37,691	7,281 (19.3%)	17,223	2,719 (15.8%)	20,468	4,562 (22.3%)	0.65 (0.62–0.69)	$P < 0.05$
Hol et al., 2012 (34)	4,407	1,092 (24.8%)	2,221	472 (21.3%)	2,186	620 (28.4%)	0.68 (0.59–0.78)	$P < 0.05$
Quintero et al., 2012 (35)	26,599	9,089 (34.2%)	12,156	4,145 (34.1%)	14,443	4,944 (34.2%)	0.99 (0.94–1.05)	$P = 0.82$
Ferrari et al., 2012 (36)	42,245	1,744 (41.3%)	20,311	7,980 (39.3%)	21,934	9,461 (43.0%)	0.85 (0.82–0.89)	$P < 0.05$
McDonald et al., 2012 (37)	66,225	38,720 (58.5%)	32,318	18,058 (55.8%)	33,907	20,662 (60.9%)	0.81 (0.79–0.84)	$P < 0.05$
Kluhsman et al., 2012 (38)	200	145 (72.5%)	50	29 (58.0%)	150	116 (77.0%)	0.40 (0.21–0.80)	$P < 0.05$
Gupta et al., 2013 (39)	1,593	648 (40.7%)	600	232 (38.7%)	993	416 (41.9%)	0.87 (0.71–1.08)	$P = 0.20$
Kelley et al., 2013 (40)	9,704	5,023 (51.8%)	4,499	2,177 (48.4%)	5,205	2,846 (54.7%)	0.78 (0.72–0.84)	$P < 0.05$

lower in studies that did not use an advance notification letter of invitation (OR, 0.77; 95% CI, 0.73–0.82; $P < 0.01$) while there was nonsignificantly lower male uptake in studies using a letter with advance notification (OR, 0.89; 95% CI, 0.64–1.23; $P = 0.47$; Table 4).

Test delivery method

Several studies ($n = 7$) required the participant to collect the test from a GP, nurse, or pharmacist, while nine studies mailed the test. Subgroup differences for test delivery methods were nonsignificant ($P = 0.65$). Male uptake was significantly lower in studies which mailed the test to participants' homes (OR, 0.79; 95% CI, 0.75–0.83; $P < 0.01$) and nonsignificantly lower in studies which required participants to collect the test (OR, 0.83; 95% CI, 0.66–1.05; $P = 0.13$; Table 4).

Screening recommendations

Eight studies used recommendations or endorsement of screening, either by a GP, nurse, or local Mayor. Subgroup differences were nonsignificant for use or nonuse of recommendations ($P = 0.54$). Those studies that provided a screening recommendation had nonsignificantly lower uptake in males (OR, 0.85; 95% CI, 0.68–1.05; $P = 0.13$) while there was significantly lower male uptake in studies that did not use recommendations (OR, 0.79; 95% CI, 0.76–0.82; $P < 0.01$; Table 4).

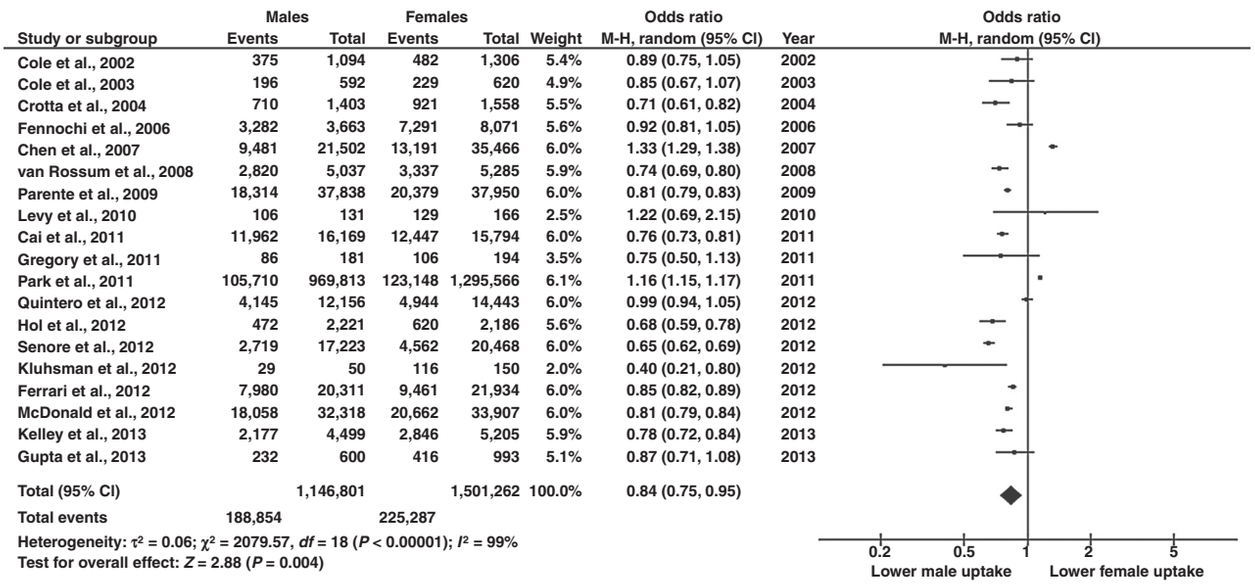

Figure 2.
Forest plot corresponding to the main random effects meta-analysis of 19 estimates quantifying the relationship between gender and uptake of FIT-based colorectal cancer screening.

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Table 3. The Newcastle–Ottawa scale of included studies: reviewers judgment

	Sample representativeness (selection)	Sample size (selection)	Counfounding controlled (comparability)	Statistical tests (outcome)	Total stars and quality rating
Park et al., 2011 (22)	*	*		*	3/6 moderate
Cole et al., 2002 (23)	*	*		**	4/6 moderate
Cole et al., 2003 (24)	*	*		**	4/6 moderate
Crotta et al., 2004 (25)	*	*			2/6 low
Fenochi et al., 2006 (26)			*		1/6 low
Chen et al., 2007 (27)	*				1/6 low
van Rossum et al., 2008 (28)	*	*		**	4/6 moderate
Parente et al., 2009 (29)	*	*			2/6 low
Levy et al., 2010 (30)				*	1/6 low
Cai et al., 2011 (31)	*	*		**	4/6 moderate
Gregory et al., 2011 (32)	*			*	2/6 low
Senore et al., 2012 (33)	*	*		*	3/6 moderate
Hol et al., 2012 (34)	*	*		**	4/6 moderate
Quintero et al., 2012 (35)	*	*		**	4/6 moderate
Ferrari et al., 2012 (36)	*	*	**		4/6 moderate
McDonald et al., 2012 (37)	*	*		*	3/6 moderate
Kluhsman et al., 2012 (38)				*	1/6 low
Gupta et al., 2013 (39)		*		**	3/6 moderate
Kelley et al., 2013 (40)	*	*		**	4/6 moderate

Screening age range

Subgroup differences were nonsignificant for screening studies targeting different age ranges ($P = 0.28$). Uptake was significantly lower in males when screening was targeted at those of ages 40 to 75 years (OR, 0.79; 95% CI, 0.74–0.84; $P < 0.01$) while uptake targeted at those of ages 50 years and over with no upper age limit was similar in males and females (OR, 0.92; 95% CI, 0.70–1.19; $P = 0.51$; Table 4).

Fenocchi and colleagues (26) and Ferrari Bravo and colleagues (36) reported uptake by age and gender. In the former, uptake was nonsignificantly lower in males in people of ages 50 to 69 years (OR, 0.93; 95% CI, 0.81–1.07; $P = 0.32$) and those of ages 70 years or older (OR, 0.71; 95% CI, 0.41–1.29; $P = 0.22$). In the latter, uptake in males was significantly lower in those of ages 50 to 59 years (OR, 0.76; 95% CI, 0.72–0.81; $P < 0.01$) and in those of ages 60 to 69 years (OR, 0.94; 95% CI, 0.88–0.99; $P = 0.02$), but did not differ in those of ages 70 71 years (OR, 1.05; 95% CI, 0.87–1.27; $P = 0.56$).

Number of FIT samples required

Fourteen studies reported the number of samples requested; 10 studies requested one sample and four requested two or three samples over varying time intervals. The subgroup differences for the number of samples required were nonsignificant ($P = 0.42$). The OR for male uptake was significantly lower in both subgroups (one sample: OR, 0.84; 95% CI, 0.71–0.98: $P = 0.03$; two/three samples: OR, 0.78; 95% CI, 0.74–0.82; $P < 0.01$; Table 4).

Screening reminders

Ten studies reported the use of reminders (varying from 2 weeks to 6 months; Table 1) and two studies reported using no reminders. Male uptake was significantly lower in both subgroups (Table 4) with no difference in these subgroups ($P = 0.51$).

Discussion

This systematic review and meta-analysis is the first to examine whether there are gender differences in uptake of FIT-based colorectal cancer screening. It provides valuable information for screening agencies relating to the implementation and delivery of program. Overall, uptake in males was 16% lower than in females, and this was statistically significant. Although there was notable heterogeneity between studies in terms of design and screening organization, as well as overall uptake, lower uptake in males persisted across subgroups by study design, setting, methods of invitation and delivery, use of recommendations, screening age range, number of samples, and use of reminders.

Of note was the similar uptake in males and females in studies based in Asia, which contrasted with studies from other settings. Studies from Asia had similar uptake in males and females, whereas studies from Europe reported lower uptake among men. Although subgroup differences were nonsignificant across countries, much of the data required for inclusion in subgroup analysis was not reported in the studies from Asia. Therefore, the possibility that cultural or social factors may be responsible for differential uptake in males and females cannot be entirely discounted. It will be interesting to observe uptake of FIT-based screening in future studies within countries in Asia in comparison with Europe and Australia.

There was also no significant difference in male and female uptake in studies of low quality. Most of these required the participant to collect the test, so the effect estimate may reflect this. Test collection from a GP clinic, pharmacist, or distribution center (nurse) requires the participant to make face-to-face contact with a health professional and may act as an encouragement or endorsement of the test in addition to providing access to information about the test and how to carry it out. Studies of low quality also had quite high overall uptake, and the effect estimate may reflect this rather than the low quality *per se*.

Although there was no formal difference in subgroups defined by whether or not there was a recommendation or endorsement of the test, it was noteworthy that uptake was only significantly lower in males than females in studies in which no recommendation was used. Other evidence suggests that lack of a doctor recommendation is an important barrier to colorectal cancer screening (41). Our findings suggest that contact with, or endorsement of the test through a health professional (GP, nurse, and pharmacist) may serve to encourage men to complete the screening test. This

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Table 4. Summary of primary and subgroup random effects meta-analysis

Subgroup	Number of studies	OR 95% CI	I^2	*P*
Primary meta analysis	19	0.84 (0.75–0.95)	99%	<**0.01**
Study quality				
Moderate	14	0.81 (0.76–0.85)	95%	<**0.01**
Low	5	0.89 (0.63–1.26)	96%	0.51
Subgroup differences		—	0%	0.58
Study design				
RCTs	6	0.83 (0.71–0.97)	91%	**0.02**
Observational	13	0.83 (0.76–0.91)	98%	<**0.01**
Subgroup differences			0%	0.99
Study setting				
Europe	9	0.78 (0.73–0.84)	95%	<**0.05**
North America	3	0.79 (0.49–1.28)	68%	0.35
Asia	3	0.97 (0.73–1.28)	100%	0.81
South America	1	0.92 (0.81–1.05)	—	—
Australia	3	0.86 (0.76–0.98)	0%	**0.03**
Subgroup differences		—	38%	0.16
Letter of invitation				
Letter without advance notification	9	0.77 (0.73–0.82)	87%	<**0.01**
Letter with advance notification[a]	3	0.89 (0.64–1.23)	92%	0.47
Subgroup differences		—	0%	0.41
Test delivery				
Test mailed	9	0.79 (0.75–0.83)	45%	<**0.01**
Test collected	7	0.83 (0.66–1.05)	99%	0.13
Subgroup differences		—	0%	0.64
Recommendation				
Recommendation provided	8	0.85 (0.68–1.05)	99%	0.13
No recommendation provided	7	0.79 (0.76–0.82)	45%	<**0.01**
Subgroup differences		—	0%	0.54
Screening age range				
40–75	14	0.79 (0.74–0.84)	92%	<**0.01**
50+ (5)	5	0.92 (0.70–1.19)	99%	0.51
Subgroup differences		—	13%	0.28
Number of samples				
1 sample (10)	10	0.84 (0.71–0.98)	99%	**0.03**
2 or more samples (4)	4	0.78 (0.74–0.82)	13%	<**0.01**
Subgroup differences		—	0%	0.42
Screening reminders				
No reminder provided	2	0.85 (0.75–0.96)	73%	**0.01**
Reminder provided	10	0.81 (0.73–0.89)	87%	<**0.01**
Subgroup differences		—	0%	0.51

NOTE: Values in bold indicate $P < 0.05$.

[a]Advance notification indicates pre-invitation letter, followed by invitation letter.

has been noted elsewhere, where male compliance with medical procedures is increased when encouraged by a medical professional (42).

Although subgroup differences were (once again) nonsignificant, studies that were not population-based did not have significantly lower uptake in males. Although the studies which were not population-based differed in many ways, in three of four the screening invitation was endorsed through a GP or GP practice while two required the participant to collect the test. Therefore it cannot be ruled out that the nonsignificantly lower uptake in males may be a result of test collection and GP recommendation.

Age is an important predictor of colorectal cancer risk. Here, male uptake was not significantly different from female uptake in studies targeting those of ages 50 years and over with no upper age limit. However, this may be a result of the fact that some studies involved test collection (3 of the 5 studies) and/or recommendations to complete the test by a GP (4 of the 5 studies), as opposed to older men being more likely to participate in screening. Further investigation is required to assess if there is differential uptake between younger and older males in FIT-based screening and, if so, what may be driving such differences.

Cole and colleagues (24) have reported that participation in their study was significantly improved (increase in relative risk of participation of 30%) through simplification of the sampling method (using two rather than three samples); this did not differ by gender, age, or socioeconomic status. In this meta-analysis, there were no subgroup differences in effect estimates according to whether studies required a single, or more, samples. Further investigation is required to assess if there is differential uptake in males and females when different FIT sampling strategies are used.

Although there is tentative evidence from this review that requiring participants to collect the test, using a GP recommendation and using an advance notification results in similar uptake in males and females, the general lack of significant subgroup differences suggest that study design or screening organization may not be the important drivers of poorer male uptake. However, these elements may help inform development of a taxonomy of compliance in particular groups, such as those based on sex or other background characteristics. Further research in identifying and expanding on such taxonomy is warranted. Given the dearth of evidence regarding reasons for nonparticipation in FIT

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screening in males and females, and the fact that FOBT and FIT may be considered somewhat similar from the point of view of screening invitees, it is worth considering what is known about drivers of home-based FOBT screening (non)participation. An early review of colorectal cancer screening uptake using FOBT reported that the main factors for noncompliance with screening were: conflicts with work or family, inconvenience, being too busy, or being away, lack of interest and costs (43). In addition, the same review reported that noncompliance was associated with having no current health problems, being too embarrassed to complete the test, feeling the test was too unpleasant, being anxious and not wanting to know the test results (43). These findings are in line with Chapple and colleagues (44) in the UK FOBT screening program.

The evidence base for reasons underlying gender-based differences in colorectal cancer screening uptake is very limited, and even less is known about uptake in FIT based screening specifically. Recently Ritvo and colleagues (45) suggested that males may procrastinate about colorectal cancer screening, but that, underlying this, is a deeper fatalism about cancer disease and a disbelief in the preventative–protective elements of screening. It has also been reported that males use primary care services less frequently than women (46) perhaps making them less inclined to be screened when offered the opportunity. In addition, White and colleagues (46) suggest that, in Europe, the general absence of male targeted health care programs may hinder men's ability to identify as participants in health care. These observations indicate that studies are now required exploring cultural norms surrounding, psychologic and other barriers to, and facilitators of, FIT screening and how these may differ between the sexes. It would be useful to explore these barriers and facilitators through theory-based research into gender differences in preventive health behaviors.

Conclusion

Uptake of FIT-based colorectal cancer screening among males is significantly lower than among females. Although studies differed in design and screening organization methods, poorer male uptake persisted throughout subgroup analysis. Further investigation is required into why men are less likely to attend FIT screening and what factors may act as barriers or facilitators to screening uptake in men and women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: N. Clarke, L. Sharp, P.M. Kearney
Development of methodology: N. Clarke, L. Sharp, P.M. Kearney
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): N. Clarke
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N. Clarke, L. Sharp, A. Osborne, P.M. Kearney
Writing, review, and/or revision of the manuscript: N. Clarke, L. Sharp, A. Osborne, P.M. Kearney
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): N. Clarke
Study supervision: L. Sharp, P.M. Kearney

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Comparison of Uptake of Colorectal Cancer Screening Based on Fecal Immunochemical Testing (FIT) in Males and Females: A Systematic Review and Meta-analysis

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Impact of gender on decisions to participate in faecal immunochemical test-based colorectal cancer screening: a qualitative study

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Abstract

***Objective*: Faecal immunochemical tests (FITs) are increasingly being used in population-based colorectal cancer-screening programmes. Uptake of FIT is lower in men than women; however, the reasons for this are not well understood. We aimed to explore gender differences in influences on decisions to participate in FIT screening.**

***Methods*: This is a qualitative study using in-depth face-to-face interviews of four groups of screening invitees (male and female screening users and male and female screening non-users), purposively sampled from the database of a population-based FIT screening programme. Recruitment continued until saturation was reached. Interviews were audio recorded and transcribed verbatim. Thematic analysis using the framework approach was employed with the theoretical domains framework guiding analysis.**

***Results*: Forty-seven screening invitees were interviewed. Six theoretical domains influenced screening uptake: 'environmental context and resources', 'beliefs about capabilities', 'beliefs about consequences', 'emotions', 'social influences' and 'knowledge'. Male non-users were often fatalistic, less knowledgeable and misinformed about cancer and FIT screening compared with other groups. Female non-users expressed negative attitudes, beliefs and emotions towards FIT screening, cancer, social influences and the medical profession and were over-confident about their health.**

***Conclusions*: Negative attitudes and emotions to screening dominated non-user decision-making but differed by gender. Opportunities to improve uptake in men and women exist. Greater national discussions on the benefits of FIT screening, and development of screening materials tackling negative attitudes and beliefs while recognising male/female differences, may improve screening uptake.**

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Background

Worldwide, colorectal cancer is the second most common cancer diagnosed in women and the third most common in men although men have higher incidence and mortality from the disease [1]. Screening is effective in reducing colorectal cancer incidence and mortality [2–7]. Current guidelines recommend population-based screening of asymptomatic people aged 50–74 years or ≥50 years annually or biennially using non-invasive methods (guaiac-based faecal occult blood test (FOBT) or faecal immunochemical test (FIT)) or every 5–10 years using other procedures (flexible sigmoidoscopy/colonoscopy) [8,9]. Many population-based screening programmes employ FOBT as the initial screening test. However, FIT is increasingly being recommended because it has higher specificity and sensitivity [8] and higher uptake [10,11].

In order to be effective in reducing incidence and mortality, population-based screening programmes require high uptake. Men have higher uptake of endoscopy-based screening procedures, while women have higher uptake of non-invasive tests such as FOBT and FIT [12–14]. For FIT specifically, a recent systematic review and meta-analysis estimated that the odds of screening participation were significantly lower in men compared with women (odds ratio, 0.84; 95% confidence interval, 0.75–0.95) [15]. However, the drivers of lower male uptake did not appear to be related to screening programme design or organisation [15].

Lower-colorectal cancer-screening uptake in men has been associated with poorer knowledge of colorectal cancer and screening [16,17], lower perceived severity of colorectal cancer, fatalistic beliefs about cancer, procrastination, lower beliefs about capabilities of

successfully completing testing and machismo and homosexual sensitivities [16,18,19]. Higher uptake in women has been associated with having a family member with colorectal cancer [20], while lower uptake has been associated with fear of endoscopic-based procedures and fear of a positive diagnosis [16]. However, this evidence relates to FOBT or endoscopic-based tests; evidence on reasons for gender differences in uptake of FIT specifically is lacking.

We used a qualitative approach to explore differences in male and female influences on use and non-use of a population-based FIT colorectal cancer-screening programme.

Methods

Design

In-depth semi-structured interviews were conducted among people invited to participate in the Tallaght Hospital/Trinity College Dublin Colorectal Cancer Screening Programme (TTC-CRC-SP), a population-based FIT-based colorectal cancer-screening programme in Tallaght, one of the most disadvantaged areas of Ireland [20,21]. Approximately 10 000 people aged 50–74 years were identified through primary care practices and invited by mail to participate in screening; the FIT kit was sent with the initial invitation. Round 1 operated during 2008–2010 (uptake was 51%) and round 2 during 2011–2012 (uptake was 47.5%) [22]. In both rounds, uptake was significantly lower among men than women (e.g. round 2: 44.5% vs 50%; odds ratio 0.79; confidence interval 0.73–0.89) [22]. The TTC-CRC-SP ceased in December 2012 after two screening rounds, and in 2013, a national FIT-based screening programme (BowelScreen) began (http://www.bowelscreen.ie).

Theoretical framework

The theoretical domains framework (TDF) [23] was used as a framework for examining potential influences on whether individuals accepted an invitation to participate in the TTC-CRC-SP. The TDF integrates 33 psychological and organisational theories to provide a comprehensive framework of possible influences on behaviour [23]. It consists of 14 domains [23]: knowledge, skills, social/professional role and identity, beliefs about capabilities, optimism, beliefs about consequences, reinforcement, intentions, goals, memory attention and decision processes, environmental context and resources, social influences, emotion and behaviour regulation.

Recruitment and interviews

A purposive sample was drawn from the TTC-CRC-SP database (Supporting Information Fig. S1). 'Users' were defined as those who had taken part in either or both screening rounds; 'non-users' did not take part in any screening round. Screening invitees were stratified into four groups according to participation status (users/non-users) and gender (male/female). Each group was sorted alphabetically in Microsoft Excel by surname and forename and a random number assigned to each person (using the RAND [Random number generator] function). We re-sorted each group from lowest to highest number and approached people in sequence, starting with the lowest numbered individual. The study was approved by the St James/Adelaide Meath Hospital incorporating the National Children's Hospital Research Ethics Committee (REC Reference 2013/12/05).

Potential interviewees were contacted by mail and invited to be interviewed. Those who returned a reply slip were telephoned by the male interviewer (NC) who answered any questions and arranged a convenient time and place for the interview. All participants provided written informed consent. Interviews were conducted face to face, at the participant's home, the local hospital or another venue, according to the interviewee's preference, during May–August 2014. Everyone who accepted and was available to take part was interviewed. Recruitment continued until saturation was reached (i.e. no new themes emerging across all interviews). Interviews were audio recorded with the interviewee's permission and lasted 15–90 min (mean = 41 min).

Topic guide

The topic guide (Supporting Information Table S1) was informed by the TDF. Questions were developed for each domain to explore potential influences on screening invitees' decisions regarding FIT screening use.

Analysis

Transcripts were imported into NVivo 9. Data were analysed thematically using the framework approach; this involved familiarisation, construction of a thematic framework (the TDF domains), indexing and sorting data and reviewing data extracts [24]. Two researchers independently read four transcripts, coded these to the TDF domains and then discussed coding to reach consensus. The remaining interviews were then coded to the TDF by one researcher (NC). A health psychologist (PG) was consulted when necessary. Domains were compared and contrasted by strata. Selected illustrative quotes are presented in Tables 1 (users) and 2 (non-users), with additional quotes in Supporting Information Tables S2 (users) and S3 (non-users).

Results

Interviews were conducted with 47 people, 28 users of FIT-based screening (16 male and 12 female) and 19 non-users (9 male and 10 female). Interviewees'

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Table 1. Illustrative quotes for domains potentially influencing screening decisions in users, by gender

Domain	Female compliers	Male compliers
Environmental context and resources	She had bowel cancer. Well, her bowel burst, actually, she's lucky to be alive. I thought, oh no, I need to get this done, because there's slight changes, do you know. (P-9)	And certainly in light of the two guys, friends of mine who are in trouble now. So I would certainly be very conscious of it. (P-28)
Beliefs about capabilities	Well, I thought so. I mean, it's pretty simple to do, just take the little stick and… It's not exactly rocket science. (P-7)	It was easy enough, yeah. Yeah, you just prepare whatever you have to do upstairs and do it. (P-32)
Beliefs about consequences	But I always feel that if you had to get a cancer, it wouldn't be one of the worst [*colorectal cancer*], because it is treatable, and if it's caught in time I think you have a better chance than you have if you got pancreatic cancer. (P-3)	If they got it in time, if they were screening, and all that, that's the way I believe in it. Well, it's like anything, I suppose, if you get it in time. (P-26)
Social influences	If I came to a bowel cancer awareness week or breast cancer or bowel cancer or whatever, it would make me think, and it's 'oh I must follow up on that and have all that checked out for myself'. (P-3)	She nagged me into it [female spouse], so I did it. (P-35)
Emotions	I thought brilliant....Great idea. Any of those tests for prevention, I would say, is a great idea. (P-1)	The more people you've met or have known that have had cancer, and the closer you are to getting it, the more frightening it becomes, especially when people die, obviously. (P-29)
Knowledge	I suppose it's one of the cancers I would think, no, you won't get that…it's just maybe to do with diet and lifestyle, is a lot to do with it probably. (P-6)	Well, at the moment, after doing this [*colonoscopy*] I think I'm okay. (P-29)

characteristics are summarised in Supporting Information Table S4.

Six TDF domains were identified as influencing interviewees' decisions on participation in FIT-based screening: 'environmental context and resources', 'beliefs about capabilities', 'beliefs about consequences', 'social influences', 'emotions' and 'knowledge' (Supporting Information Table S5).

Environmental context and resources

Screening users

A prominent influence on screening behaviours was salient events in interviewees' lives. These acted as a catalyst encouraging screening participation in male and female users. Generally, these related to others diagnosed with cancer or other gastric/bowel conditions and were a context within which screening was validated as a positive health behaviour.

Resources and materials relating to the FIT kit also influenced participation. Most female users found the test equipment simple and easy to use. In a few instances, women raised concerns with the kit (e.g. paper for catching stool, sampling tool and packaging for storing the sample in the refrigerator); these issues were overcome and did not act as barriers to participation. Male users were very positive about the screening resources and materials provided.

Screening non-users

Female non-users referred to salient events related to colorectal cancer, other cancers or other gastric conditions; these events were seen in a negative light and presented as reasons not to participate (Table 2). Male non-users

Table 2. Illustrative quotes for domains potentially influencing screening decisions in non-users, by gender

Domain	Female non-compliers	Male non-compliers
Environmental context and resources	I got it the morning after my young fellow nearly died the night before and I just… I'm sick of hospitals…and it was all bowels. (P-19)	So I just kept putting it off. I mean, in and out of the courts for the last… I mean, I'm going to the High Court now [*custody battle*]. So I've been down the courts for the last 12 years. (P-45)
Beliefs about capabilities	Well, when I saw what you had to do, I couldn't cope with that [*faecal sampling*]. (P-15)	Yeah…I'd do it myself now. I've no problem doing it now. (P-39)
Beliefs about consequences	It'd probably be fairly invasive and end up with bags and all sorts of things. (P-18)	I'd say they'd be dead. Because there's no cure for cancer is there, not that I know of anyway. (P-47)
Social influences	Well, it was my mother, when I got the letter my mother said, 'Throw that in the bin, you don't want to know anything about yourself.' (P-16)	And she [*wife*] said to me, 'Did you do it?' 'Aye,' I said. But I didn't. (P-46)
Emotions	I thought, 'I'm not doing that' [*faecal sampling*]. Yes… If it had been probably- oh God, it sounds disgusting. (P-13)	At the time it was, yeah, it was a fear of dying. (P-47)
Knowledge	That would have been on my mind, opening that pack, and looking at it and thinking, 'Well, I don't have the symptoms that [sister] had. If I have, I'll go.' (P-22)	But you wiped your bottom and you sent this piece of paper off to the…wherever, the lab. (P-40)

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also mentioned salient events acting as barriers to screening; these were generally unrelated to medical matters or illness (e.g. relationship breakdown and child custody battle).

Uniquely, female non-users had poor trust in the medical profession, particularly their local hospital, and this influenced their decision not to take part. Some male non-users had issues with the environmental context, specifically delivery of mail, implying the screening invitation did not reach them.

Female non-users' attitude to FIT test materials was often negative and related to the sampling kit (e.g. catching of the stool using the paper provided and using the sampling stick) and packaging for storing the sample in their refrigerator (e.g. concerns about food contamination). Male non-users had few or no issues with the resources and material.

Beliefs about capabilities

Screening users

Both male and female users had strong confidence in their ability to do the test, describing how they carefully followed the test instructions and pointing out 'it's not rocket science'.

Screening non-users

Male non-users generally believed they would have had no problems conducting the test despite not participating. Female non-users raised several issues impacting on their perceived ability to carry out the test, including an inability to deal with faecal matter and lack of confidence in sampling stool with the equipment provided. Others suggested that they felt confident to recognise illness in themselves observing that they did not participate in screening because they felt they were not ill or that they had no bowel symptoms; several made statements such as 'you know your own body' and 'if it's not broke don't fix it'.

Beliefs about consequences

Screening users

Both female and male users were very positive about the implication of a colorectal cancer diagnosis, often stating that they considered that early detection is the key to successful treatment.

Screening non-users

Both female and male non-users were generally negative about the implication of a colorectal cancer diagnosis. Many female non-users discussed undergoing surgery and the potential need for a colostomy bag in negative terms. Male non-users often held fatalistic beliefs that a diagnosis inevitably resulted in death.

Social influences

Screening users

Male users spoke about the positive influence of female partners in their decision to participate. Female users discussed social influences outside the family on their screening participation including the impact of media campaigns for other cancer screening and quitting smoking.

Screening non-users

Female non-users raised a range of social influences that were generally negative and influenced their decision not to participate in screening (e.g. a neighbour who experienced colonoscopy-related complications, lack of encouragement from one's General Practitioner (GP) and discouragement by one's mother). While there were fewer social influences on male non-users' screening decisions, some discussed a female relative's unsuccessful attempt to encourage them to participate.

Emotions

Screening users

Male and female users spoke of their decision to be screened with positive emotional affect feeling it was a 'brilliant idea'. Although male users sometimes mentioned fear of cancer and embarrassment (with respect to the test), these did not inhibit their participation. Instead, fear of cancer was a catalyst to screening, providing 'peace of mind' in knowing that one has a 'pretty good chance of not getting it'.

Non-users

Female non-users expressed negative emotions around screening including disgust (related to handling faeces or storing the sample in the fridge), anger (timing, e.g. receiving test while grieving a spouse's death) and fear (of cancer). Some female non-users described emotional burnout due to other conditions leaving them emotionally unequipped to deal with a potential colorectal cancer diagnosis, leading them to decide not to participate. Male non-users expressed negative emotions relating to a fear of cancer, and dying (considered as potential consequences of screening) influencing their decision not to participate.

Knowledge

Screening users

Generally, female users considered their risk of developing colorectal cancer as low, based on their family history of the disease and lifestyle (which they considered 'healthy'). Some male users considered they had low risk because they had previously had a colonoscopy (either having a negative result or polyps removed) and therefore

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were in no immediate danger or because they had a healthy diet and lifestyle; others considered that they had high risk because of other gastrointestinal conditions (e.g. Crohn's disease). Overall, users had a very considered view of their colorectal cancer risk and felt screening participation would sustain a low risk or reduce a high risk. Male and female users often knew other people with colorectal cancer, and this motivated them to participate in screening.

Screening non-users

Female non-users generally believed that their risk was low, mainly because they had no family history or symptoms of the disease (generally understood as frequent bowel motions). This perceived low risk led them to believe they did not need to be screened. Male non-users generally stated they did not know their risk of developing colorectal cancer and were often unsure if they knew anyone with colorectal cancer.

Female non-users were often unclear about the screening procedure and sometimes described having not read the information sent with the test kit. Male non-users stated that they were clear about how the test was carried out but upon discussion, several had misunderstood how to complete it.

Discussion

We used qualitative methods to explore influences on men and women's decisions to participate in FIT-based colorectal cancer screening. Considering FIT-based screening is increasingly being used in population-based programmes and that uptake is variable (19–76% in population-based programmes, average 44% [15]); this study provides valuable information on factors influencing non-participation, examining these differences by gender. Six TDF domains emerged as influencing individuals' decisions on FIT-based screening participation. Although all of these domains were evident for users and non-users, issues within domains differed between groups, or the same issues played out differently in the two groups and sometimes by gender.

Negative attitudes, beliefs and emotions pervaded decisions of non-users, while positive attitudes, beliefs and emotions were evident among users. Negative attitudes are associated with lower colorectal cancer screening participation [25,26]. Our study found differences in these attitudes and beliefs by gender especially among male and female non-users. These included differences in salient events (medical matters in women and non-medical matters in men), response to materials and resources (test kit, storage and faecal sampling in women and non-test-related factors in men), perceived consequences of screening and diagnosis (men's fatalism) and social influences (negatively impacting on women's decisions, but less apparent in males).

Fear of cancer and fatalistic beliefs result in low adherence to screening recommendations [27], but fear may have different effects on screening decision-making around participation [28]; this has not been explored by gender. In our study, although male users had some fear around a cancer diagnosis, this did not impede participation, whereas in non-users, fear was an impediment to screening. Fatalism has been associated with poor screening uptake [19,29–31], and those with greater fatalistic beliefs are more likely to believe they have a greater risk of cancer and that it is a more severe disease [31]. Where our study extends these are that we found; fatalistic beliefs were present among male non-users only and influenced their decision not to participate.

Non-users, particularly male non-users, had poorer knowledge of colorectal cancer than users and less often knew of others with cancer. Knowledge about cancer generally, and knowing someone with colorectal cancer, is positively associated with screening intention and participation [25,32,33], while low health literacy has been identified as influencing non-participation [34]. Our findings suggest that health literacy and social supports that provide opportunities to learn about illnesses or screening may be especially poor among male non-users thereby influencing non-participation. Von Wagner *et al.* [35] have suggested the use of a wider range of communication strategies in raising awareness of screening, and we concur with this.

Disgust influenced women's, but not men's, decisions to participate in screening. Different forms of disgust, such as trait disgust (the stable tendency to experience disgust) and state disgust (current emotional experience), might influence particular types of decisions such as taking part in screening. A recent study found that while women had higher scores for both forms of disgust, between-gender differences were not significant, but the authors acknowledged methodological limitations [36]. There is a need for research identifying how screening information could address anticipated disgust [36,37], and our finding suggests this should be considered with gender differences in mind.

There were few differences between male and female users in influences on screening decisions, but female relatives often influenced male users' decisions to be screened, but this influence did not operate in the other direction. Spouses play an important role in colorectal cancer screening decision-making [38,39], and women have been described as the guardians of men's health [40]; our study appears to be the first to show that this positive influence operates only for men. Among male non-users, while social influences were fewer, female relatives had sometimes attempted to influence them, albeit unsuccessfully. Further investigation of female influence on male screening decision-making is warranted.

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Male non-users were less clear about their non-participation than female non-users, citing external circumstances or that they had forgotten or did not have time. Those who cited external circumstances or forgetting as reasons for non-participation could have been masking their true reasons. Elsewhere, it has been reported that unscreened men often procrastinated about screening, being vague and emotionally distant around screening decisions [19]. In our study, a small number of male non-users revealed that they unconsciously resisted doing the test because of an underlying fear of the potential outcome of screening. Further investigation on resistance to screening in men is warranted.

This is the first study to employ the TDF within a qualitative study investigating influences on FIT-based colorectal cancer-screening decisions. Although interviewees were recruited from a population-based screening programme, this operated in a specific area in one city, and it is possible that themes/influential domains may not generalise to other settings/populations. Our sample was drawn from a screening programme that had finished 2 years prior to recruitment, and interviewees may have had difficulty with recall, although we provided recall aids. One (male) interviewer conducted all interviews, and while this provided consistency across interviews, it is possible that the interviewer's gender influenced interviewees' responses. Finally, while we reached saturation of themes across the entire dataset, and in all strata except male non-users, the relatively small number of non-users who were interviewed is a limitation. Recruitment of non-users was challenging: 550 individuals were approached in order to obtain interviews with 19 people. It is possible that if more non-users had participated, further domains might have been identified as influencing screening decisions.

Conclusions

Our study provides novel information on influences on FIT uptake in men and women. Further investigation is required of whether and how the influences identified in this study operate independently and together at the population-level. Our findings may be used to inform the development of gender-specific interventions designed to improve uptake in FIT-based screening programmes. Moreover, the opportunity exists, within Ireland at least, where colorectal cancer screening is relatively new, to open a national discussion on the benefits of FIT-based screening, tackling the issues raised in this study and ultimately seeking to improve screening participation in both genders.

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Conflict of interest

The authors have declared no conflicts of interest.

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The role of area-level deprivation and gender in participation in population-based faecal immunochemical test (FIT) colorectal cancer screening

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ABSTRACT

This study aimed to investigate the effects of sex and deprivation on participation in a population-based faecal immunochemical test (FIT) colorectal cancer screening programme. The study population included 9785 individuals invited to participate in two rounds of a population-based biennial FIT-based screening programme, in a relatively deprived area of Dublin, Ireland. Explanatory variables included in the analysis were sex, deprivation category of area of residence and age (at end of screening). The primary outcome variable modelled was participation status in both rounds combined (with "participation" defined as having taken part in either or both rounds of screening). Poisson regression with a log link and robust error variance was used to estimate relative risks (RR) for participation. As a sensitivity analysis, data were stratified by screening round. In both the univariable and multivariable models deprivation was strongly associated with participation. Increasing affluence was associated with higher participation; participation was 26% higher in people resident in the most affluent compared to the most deprived areas (multivariable RR = 1.26: 95% CI 1.21–1.30). Participation was significantly lower in males (multivariable RR = 0.96: 95%CI 0.95–0.97) and generally increased with increasing age (trend per age group, multivariable RR = 1.02: 95%CI, 1.01–1.02). No significant interactions between the explanatory variables were found. The effects of deprivation and sex were similar by screening round. Deprivation and male gender are independently associated with lower uptake of population-based FIT colorectal cancer screening, even in a relatively deprived setting. Development of evidence-based interventions to increase uptake in these disadvantaged groups is urgently required.

1. Introduction

Colorectal cancer is the second most common cancer diagnosed in women and the third in men worldwide (Globocan, 2012). Worldwide men have higher incidence (world age standardised rate (ASR) 20.6 vs. 14.3) and mortality (ASR 10.0 vs. 6.9) from the disease (Globocan, 2012). Higher mortality has also been observed among lower socio-economic groups in the US and Europe (Manser and Bauerfeind, 2014).

Screening is efficacious and effective in reducing colorectal cancer incidence and mortality in the population (Atkin et al., 2010; Brenner et al., 2014a, 2014b; Burch et al., 2007; Hewitson et al., 2008; National Cancer Institute, 2012). A range of screening tests are available, which detect either pre-malignant adenomatous polyps or colorectal cancers, including endoscopic-based procedures (colonoscopy and flexible sigmoidoscopy) and faecal-based tests (faecal occult blood test (FOBT) and faecal immunochemical tests (FIT)). Current guidelines recommend population-based screening of asymptomatic people aged 50 years and over on an annual or biennial basis using non-invasive methods (FOBT or FIT) or every 5 to 10 years using other - invasive - approaches (flexible sigmoidoscopy or colonoscopy) (European Colorectal Cancer Screening Guidelines Working Group et al., 2013; Levin et al., 2008). Screening programmes require high uptake among their target population in order to maximise the health benefits, (Essink-Bot and Dekker, 2015; European Colorectal Cancer Screening Guidelines Working Group et al., 2013; Weller et al., 2009) and uptake of non-invasive methods is generally higher than invasive methods (Khalid-de Bakker et al., 2011). Therefore, many population-based screening programmes use FOBT as the initial screening test. However, FIT is increasingly being recommended as it has higher sensitivity and specificity, does not require dietary and medicinal restriction (European Colorectal Cancer

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Screening Guidelines Working Group et al., 2013; Levin et al., 2008) and has been associated with higher uptake than FOBT-based screening (Digby et al., 2013; Vart et al., 2012). Nevertheless, in current FIT-based screening programmes uptake remains low overall (Clarke et al., 2015). Moreover, uptake is significantly lower among men than women and a recent systematic review concluded that screening programme design or organisation (i.e. use of letters of invitation, use of screening recommendation, test delivery methods, use and number of reminders, number of samples required and screening age range) do not appear to be the important drivers of lower male uptake (Clarke et al., 2015). Given the differences observed in uptake in males and females in Europe, Australia and Asia (significantly lower male uptake in Europe and Australia but similar uptake in males and females in Asia) it is possible that other gender-specific socio-cultural factors may be important in influencing screening acceptability.

In the UK socio-economic deprivation has been shown to affect participation in FOBT-based colorectal cancer screening (von Wagner et al., 2011). Results from a Scottish study showed that use of FIT as the primary screening test improved uptake compared to FOBT, particularly among the most deprived and men, although many participants had been exposed to FOBT for a number of years prior to the offer of FIT (Digby et al., 2013). As far as we are aware these are the only studies that have examined how FIT might reduce disparities over FOBT screening. In addition relatively little is known about whether there are deprivation gradients in uptake of FIT-based screening and, in particular, whether gender and deprivation might operate independently in influencing participation.

Understanding socio-demographic predictors of screening participation is important because unequal access across groups runs the risk of creating or widening health inequalities (Wardle et al., 2015a). During 2008–2012 a population-based FIT-based screening programme ran in Tallaght, a district of Dublin (McNamara et al., 2014). In this setting, we investigated the effect of sex and deprivation on FIT-based screening uptake.

2. Methods

2.1. Study setting

Tallaght is one of the largest towns in the County of Dublin and has a population of just under 70,000 people (CSO, 2011). The area is identified as one of the most disadvantaged in Dublin (and, therefore, in Ireland). Ireland has a mixed public-private healthcare system. Care within the public system is available to all citizens. Unless an individual has a "medical card" (which is available to those on reduced means) they must pay to see a GP and make modest co-payments for hospital in-patient and out-patient services. Just under half of the population have private health insurance; this generally covers hospital care. The screening programme, and any associated follow-up investigations or treatment, was provided free of charge to all invitees.

The Tallaght Hospital/Trinity College Dublin Colorectal Cancer Screening Programme (TTC-CRC-SP) offered two rounds of biennial screening. 9785 individuals between the ages of 50–74, and resident in Tallaght, were identified through seven primary care practices and invited to participate in screening (Engling and Haase, 2013). Individuals were sent a FIT kit with an initial invitation letter. The invitation pack also contained information on colorectal cancer and an Irish Cancer Society help-line telephone number was also provided. The programme was not promoted beyond the invitation letter; therefore all invitees received identical information. Participation in the programme was free to all participants, as was treatment if cancer was detected. Reminders were sent to non-responders. The first screening round was completed during 2008–2010 and the second during 2011–2012. At the commencement of round two individuals were excluded if they had left the catchment area after round one, had been diagnosed with colorectal cancer in round one or were known to have died. Non-responders to round one invitation were included sent an invitation to participate in round two.

For analysis we included the available explanatory variables which were sex, age and deprivation category of the area in which the individual lived (Engling and Haase, 2013). The National Cancer Registry geocoded the addresses of residence of those invited to participate in the TTC-CRC-SP, in order to enable individuals to be assigned to an area-level deprivation category based on the Pobal Haase Pratschke (HP) Deprivation index (Engling and Haase, 2013). This index (based on the 2006 and 2011 census waves), which is assigned to small areas, is based on the following characteristics of the population resident in the area: population density, age dependency ratio, lone parent ratio, primary education only, third level education, unemployment rate and proportion living in local authority rented housing (Engling and Haase, 2013). The index is divided into 8 categories ranging from extremely disadvantaged to extremely affluent. Age (at completion of the two screening rounds) was divided into five categories for analysis: (i) <60, (ii) 60–64, (iii) 65–69, (iv) 70–74 and (v) 75+. As all invitees were included in both rounds some invitees were older than the initial screening criteria age range at the outset of round 2 (i.e. those who were aged 74 years during round 1 were aged 75 or over during invitation to round 2).

The outcome variable was uptake status (participant or non-participant) and the primary analysis was based on the two screening rounds combined. In the primary analysis, participants were defined as those who took part in either or both screening rounds; non-participants took part in neither round. Uptake was calculated as the percentage of individuals who completed a screening test out of the total number invited to participate. We excluded individuals from the analysis if: they had died prior to screening; they self-referred to screening; they were medically unsuitable for screening; the recorded address was incorrect; or a deprivation category could not be assigned to their address (Fig. 1). A sensitivity analysis was undertaken to investigate uptake separately by screening round.

All analysis was conducted using Stata 11. We compared characteristics of participants and non-participants using chi-square tests. As the outcome was common (>10%), (Bonita et al., 2006) we did not use logistic regression for estimation, rather we modelled participation status using Poisson regression with a log link and robust error variance (Zou, 2004) to estimate relative risks (RR) for participation. All three explanatory variables were fitted separately, then simultaneously. Variables were included in the final multivariable model if the p value from the associated Wald test was <0.05. We tested for interactions between the explanatory variables by fitting cross-product terms to a model containing all main effects.

Three sensitivity analyses were conducted. We stratified the data by screening round and analysed the following three outcomes separately: uptake in round 1 (participants in round 1 vs. non-participants in round 1); uptake in round 2 (participants in round 2 vs. non-participants in round 2); and uptake in both rounds (participants in both rounds vs. non-participants in either round (those who participated in only one round of screening were excluded from this sensitivity analysis)) (Fig. 1).

3. Results

Table 1 summarises the characteristics of the 9151 screening invitees included in the analysis. Of these, 46% were male. The mean age at the end of screening was 62 years (Inter Quartile Range (IQR): 57–66. Invitees were resident in only five of the eight possible deprivation categories (very disadvantaged, disadvantaged, marginally below average, marginally above average and affluent). None of the study participants were resident in areas classified as extremely disadvantaged, very affluent and extremely affluent (Engling and Haase, 2013); and almost half (48%) were from very disadvantaged or disadvantaged areas.

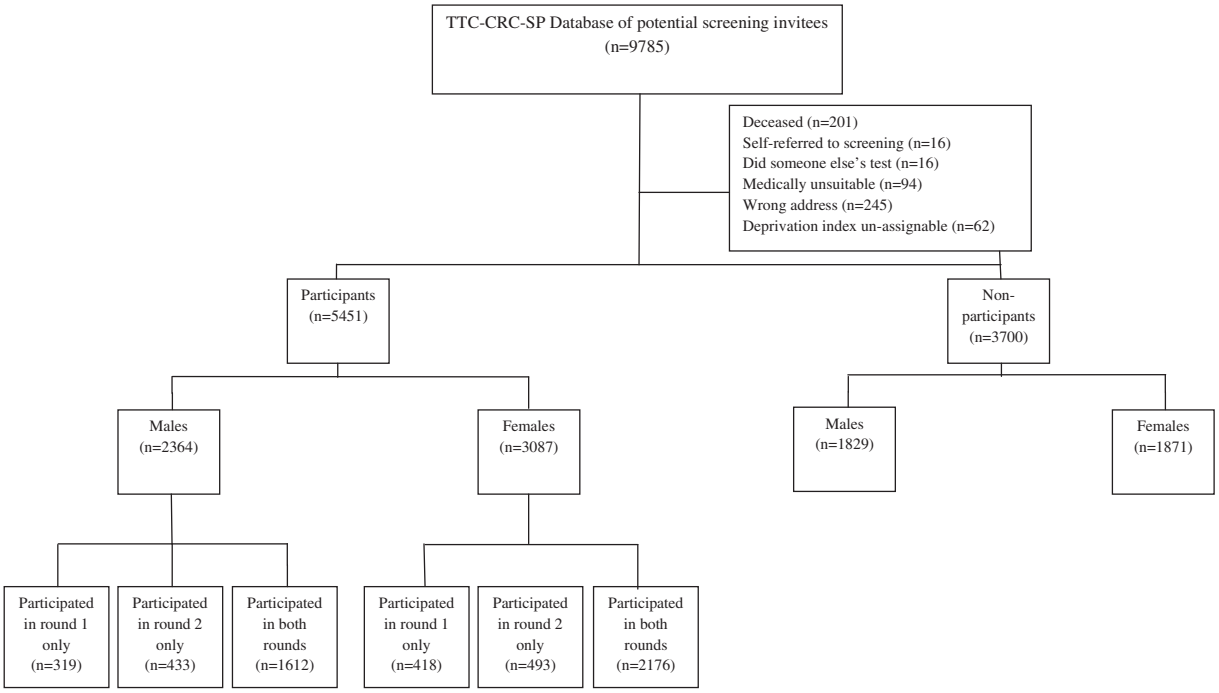

Fig. 1. Consort diagram of TTC-CRC-SP.

Overall, uptake in males was significantly lower than uptake in females ($p < 0.001$). This was also seen for round one only ($p = 0.002$). There was no difference in uptake in males and females in round two only ($p = 0.146$). Among invitees, the distribution of deprivation did not differ by sex ($p = 0.145$; similar to the national population (CSO, 2014)) but the distribution of age did ($p = 0.002$); 38% of female invitees were aged <60 compared to 35% of males, with a slightly higher proportion of males in the 70–74 age group (13% vs 11%).

Uptake in both screening rounds combined was 60%; 41% of invitees took part in both rounds, 8% in round 1 only and 10% in round 2 only; 40% did not take part in either round. A higher percentage of females participated in screening (both rounds combined: females 62% vs. males 56%) (Table 1). This translated into a significantly lower relative risk of participation in males than females in univariable analysis (RR = 0.96: 95% Confidence Interval (CI) 0.95–0.98) (Table 2). Uptake was significantly higher in all age groups compared to those aged less than 60 (Test of linear trend across groups: RR = 1.02: 95%CI 1.01–1.02; p (trend) < 0.001) (Table 2). Deprivation was strongly associated with uptake; compared to those in very deprived areas the relative risk for those resident in affluent areas was 1.22 (95% CI 1.17–1.27; Table 2). In a test for trend the relative risk of uptake increased by 6% for each category of increasing affluence (RR = 1.06: 95% CI 1.05–1.06; p (trend) < 0.001).

Table 1
Characteristics of screening invitees.

Participant characteristics	Total		Male		Female	
	N	(%)	N	(%)	N	(%)
Participation						
Participation overall	5451	(60)	2364	(56)	3087	(62)
Both rounds	3788	(41)	1612	(38)	2176	(44)
Round 1 only	737	(8)	319	(8)	418	(8)
Round 2 only	926	(10)	433	(10)	493	(10)
Non-participant	3700	(40)	1829	(44)	1871	(38)
Age[a]						
Mean age (IQR[b])	62	(57–66)	62	(58–67)	61	(57–66)
<60	3276	(37)	1419	(35)	1857	(38)
60–64	2633	(30)	1212	(30)	1421	(29)
65–69	1899	(21)	896	(22)	1003	(21)
70–74	1048	(12)	522	(13)	526	(11)
75+	66	(1)	27	(1)	39	(1)
Deprivation[c]						
Very disadvantaged	1193	(13)	521	(12)	672	(14)
Disadvantaged	3068	(34)	1374	(33)	1694	(34)
Marginally below average	3851	(42)	1800	(43)	2051	(41)
Marginally above average	872	(10)	416	(10)	456	(9)
Affluent	167	(2)	82	(2)	85	(2)

[a] Age was not available for 229 invitees.
[b] IQR: Inter quartile range.
[c] Missing categories from POBAL HP deprivation index: Extremely Disadvantaged, Very Affluent and Extremely Affluent.

In the multivariable model sex remained a significant predictor of uptake after adjusting for deprivation and age; males had a 4% lower relative risk of participation than females (RR = 0.96: 95% CI 0.95–0.97; Wald test $p < 0.001$)). Age was also a significant predictor of uptake (Wald test $p < 0.001$); those in older age groups had higher relative risks of participation than those aged <60 (although the effect was not significant in those aged over 75). In a test for trend, uptake increased by 2% (RR 1.02: 95% CI 1.01–1.02; p (trend) < 0.001) for each increasing age category. Deprivation was a strong predictor of uptake (Wald test $p < 0.001$) and the relative risk of participation was 26% higher in those resident in affluent compared to very disadvantaged areas (RR = 1.26: 95% CI 1.21–1.30) (Table 2). In a test for trend, the relative risk of uptake increased by 6% per unit increase in affluence (RR = 1.06: 95%CI 1.05–1.07). Therefore the effect of deprivation was not attenuated by age or sex. No significant interactions were found between the socio-demographic variables (age*sex; p (interaction) = 0.35; sex*deprivation; p (interaction) = 0.16; deprivation*age; p (interaction) = 0.17) (data not shown).

In the sensitivity analysis, the effects of deprivation and sex were most pronounced in screening round 1. For round 1, relative risk of participation was more than three-times higher in those resident in affluent compared to very deprived areas (multivariable RR = 3.32: 95% CI 2.28–4.83) and males had almost 20% lower relative risk of participation than females (multivariable RR = 0.81: 95% CI 0.71–0.92). For round 2, deprivation was a significant predictor of uptake, but sex was not. Participation in both rounds was significantly associated with

Table 2
Absolute uptake by participant characteristics (numbers and %) and univariable and multivariable relative risks (RR) for participation in FIT-based colorectal cancer screening with 95% confidence interval and p values: primary analysis based on two screening rounds combined.[a]

	Invited	Participated		Univariable model		Wald	Multivariable model[b]		Wald
	N	N	(%)	RR	95%CI	p	RR	95%CI	p
Sex									
Female	4958	3087	(62)	1.00	–		–	–	
Male	4193	2364	(56)	0.96	0.95–0.98	<0.001	0.96	0.95–0.97	<0.001
Age									
<60	3276	1874	(57)	1.00	–		–	–	
60–64	2633	1618	(61)	1.03	1.01–1.04		1.03	1.01–1.04	
65–69	1899	1260	(66)	1.06	1.04–1.08	<0.001	1.06	1.04–1.08	<0.001
70–74	1048	650	(62)	1.03	1.01–1.05		1.03	1.01–1.05	
75+	66	44	(67)	1.06	0.99–1.14		1.05	0.98–1.12	
Test of trend[c]				1.02	1.01–1.02		1.02	1.01–1.02	
Deprivation									
Very disadvantaged	1193	548	(46)	1.00	–		–	–	
Disadvantaged	3068	1643	(54)	1.05	1.03–1.08		1.06	1.04–1.08	
Marginally below average	3851	2542	(66)	1.14	1.11–1.16	<0.001	1.14	1.12–1.16	<0.001
Marginally above average	872	588	(67)	1.15	1.12–1.18		1.16	1.13–1.19	
Affluent	167	130	(78)	1.22	1.17–1.27		1.26	1.21–1.30	
Test of trend[c]				1.06	1.05–1.06		1.06	1.05–1.07	

[a] Participation defined as taking part in either or both screening rounds.
[b] Mutually adjusted for sex, age and deprivation
[c] Linear trend across categories.

affluence (affluent vs. very deprived multivariable RR = 2.34: 95% CI 2.04–2.67), female sex (males vs. females multivariable RR = 0.87: 95% CI 0.83–0.91), and older age (over 75 vs. <60): multivariable (RR = 1.22: 95% CI 1.07–1.39) (Supplementary Table 1).

4. Discussion

Poor screening uptake and socio-economic status are a largely unmet challenge in research and threaten potential increases in inequalities in cancer mortality (Wardle et al., 2015a). Our study shows - for the first time as far as we are aware - that deprivation is the strongest socio-demographic predictor of uptake in population-based FIT-based screening. This effect remained after adjustment for gender and age, and persisted across screening rounds. Given that our study was based in a predominantly deprived area of a large European city it was also notable that there was a significant difference in uptake even within the least affluent sectors in our study population (i.e. uptake was significantly higher among people resident in disadvantaged compared to very disadvantaged areas). A nationwide FIT-based screening programme, BowelScreen, began to roll-out in Ireland in late 2013 (www.bowelscreen.ie). Given our study was conducted in an area which does not contain the extremes of the deprivation index (i.e. extremely deprived and extremely affluent) we would speculate that, in BowelScreen, the differences in uptake observed may be even larger than those seen in our study.

Associations between poor uptake of colorectal cancer screening (using a range of tests other than FIT) and lower socioeconomic status (measured at both the individual and area level) have been reported in the literature (Gimeno García, 2011; Javanparast et al., 2010; Solmi et al., 2015; von Wagner et al., 2011; Walsh et al., 2012). Our results are consistent with – and extend - these. Others have found that, overall, FIT-based screening is usually associated with higher uptake than FOBT-based screening (which has traditionally been used in population based screening programmes) (Vart et al., 2012). If we compare uptake rate by area –level deprivation category in this study, with those reported in the English FOBT-based screening programme, rates in the current study exceed those in England in every deprivation category. While some caution is needed here, as the deprivation indices and categorisations differ in the two populations, our findings tentatively suggest that use of FIT may result in higher uptake (compared to FOBT-based screening; (von Wagner et al., 2011)) even among those resident in more deprived areas.

Solmi et al. found that after controlling for several socio-demographic, economic and health variables there was an independent association between limited wealth and lower probability of participation in colorectal screening (Solmi et al., 2015). In a decomposition analysis the authors report that health literacy contributed to 8% of the inequality in screening uptake; inadequate health literacy was associated with lower screening uptake and this was independent of individual-level measures of socio-economic status (Solmi et al., 2015). Health literacy is the degree to which individuals have the capacity to obtain, process and understand basic health information and services in order to make appropriate health decisions (Institute of Medicine (US) Committee on Health Literacy, 2004). Educational attainment and social status are positively associated with health literacy (Sørensen et al., 2015). While we did not have data on education in our study, data is available on the levels of educational attainment for the area in which our study was carried out. More than one-third (33%–39% across sub-areas) of the adult population of Tallaght have only primary education, more than twice the national average (16%; Engling and Haase, 2013). In the UK having adequate health literacy has been associated with higher participation in FOBT-based colorectal cancer screening (OR = 1.20: 95% CI 1.00–1.44) (Kobayashi et al., 2014). Von Wagner et al. have suggested that written invitations, the route through which individuals are invited to participate in colorectal cancer screening in the UK, may be difficult to process and understand for adults with limited health literacy (von Wagner et al., 2009). In our study individuals were invited to participate in writing and the invitation contained a printed leaflet with information about the screening test and how to complete it. However the possibility does exist that differences in health literacy between those resident in deprived and more affluent areas could explain some of our findings. While health literacy is correlated with reading ability they are different. Further research on uptake, education, reading and health literacy is warranted in exploring the potential underlying mechanisms of poorer uptake in males and more deprived areas in this screening population.

Our study also shows that male sex is associated with lower relative risk of participating in FIT-based screening and that this effect is independent of age and deprivation. This extends findings from our recent systematic review which observed that men had lower FIT uptake in almost every setting, but which was unable to determine if this effect was

independent of other socio-economic factors (Clarke et al., 2015). Men in Ireland have significantly poorer health literacy and functional literacy than women, (Doyle et al., 2012) suggesting that health literacy could also explain the observed lower uptake in men. However, other factors could be in operation. For example, Miles et al. have reported that poor self-rated health significantly mediated the relationship between uptake and socio-economic status (Miles et al., 2011). In a qualitative study nested within the TTC-CRC-SP, we found that several factors appeared to influence non-use of FIT-based screening, and that these factors differed by gender; drivers of non-participation in males included fear of cancer, fatalism, lack of knowledge and being misinformed whereas negative attitudes, beliefs, emotions and social influences influenced females non-use (Clarke et al., 2016). In a study on late stage colorectal and lung cancer diagnosis, females had higher fatalism scores than males, (Lyratzopoulos et al., 2015) and those with lower income and lower educational attainment also had higher levels of fatalism. Other studies have found associations between cancer fatalism, lower income/educational attainment, poor self-rated health (Miles et al., 2011; Powe and Finnie, 2003) and lower screening uptake. We have also found differences in fatalistic beliefs in our qualitative work in this population (Clarke et al., 2016) suggesting differences may exist at the screening population level in cancer fatalism between men and women (or, indeed by deprivation status). This however needs to be investigated further.

However, these explanations are speculative and further research is required to better understand what underlies the observed differences in uptake. It would be particularly useful to examine if a gender difference exists in screening information comprehension and subsequent decisions to participate in FIT-based screening – both in Ireland and more widely. It is important also to understand the mechanisms by which fatalistic beliefs and lack of cancer knowledge (which are not necessarily exclusive of one another) may contribute to low screening uptake and how these may differ by sex and socio-economic status. Some evidence is beginning to emerge on success in intervention trials aimed at tackling the socioeconomic gradient in colorectal cancer screening uptake through mailed materials (Wardle et al., 2015b). Future investigations should examine if poorer health literacy in males (and/or the most disadvantaged groups of the population) may be amenable to interventions to improve screening uptake in this population. In the meantime, we concur with von Wagner et al. (2009) that screening programmes should seek to simplify messages and make screening information more accessible to different sectors of the population.

Our study had several limitations. Firstly there was limited data available to us and the variables on which we did have information were not modifiable. In addition screening history was not available to us and as such we could not determine the extent to which prior screening may have influenced uptake. However when the TTC-CRC-SP started, no other organised colorectal screening programme was in operation in Ireland, so any previous related tests participants may have had would have been opportunistic or diagnostic. We were also unable to determine any effect of multiple invitations in individual households on uptake.

In conclusion, our study shows that FIT-based screening uptake is lower in more deprived sectors of the population and in men, and that these are independent effects. It is important to investigate what underlies these findings to inform the development of interventions to reduce and, ideally, eliminate these disparities. Failure to intervene effectively will ultimately mean that these groups will experience a disproportionately greater burden of colorectal cancer.

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Conflicts of interests

The authors declare no conflicts of interest with respect to this article.

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